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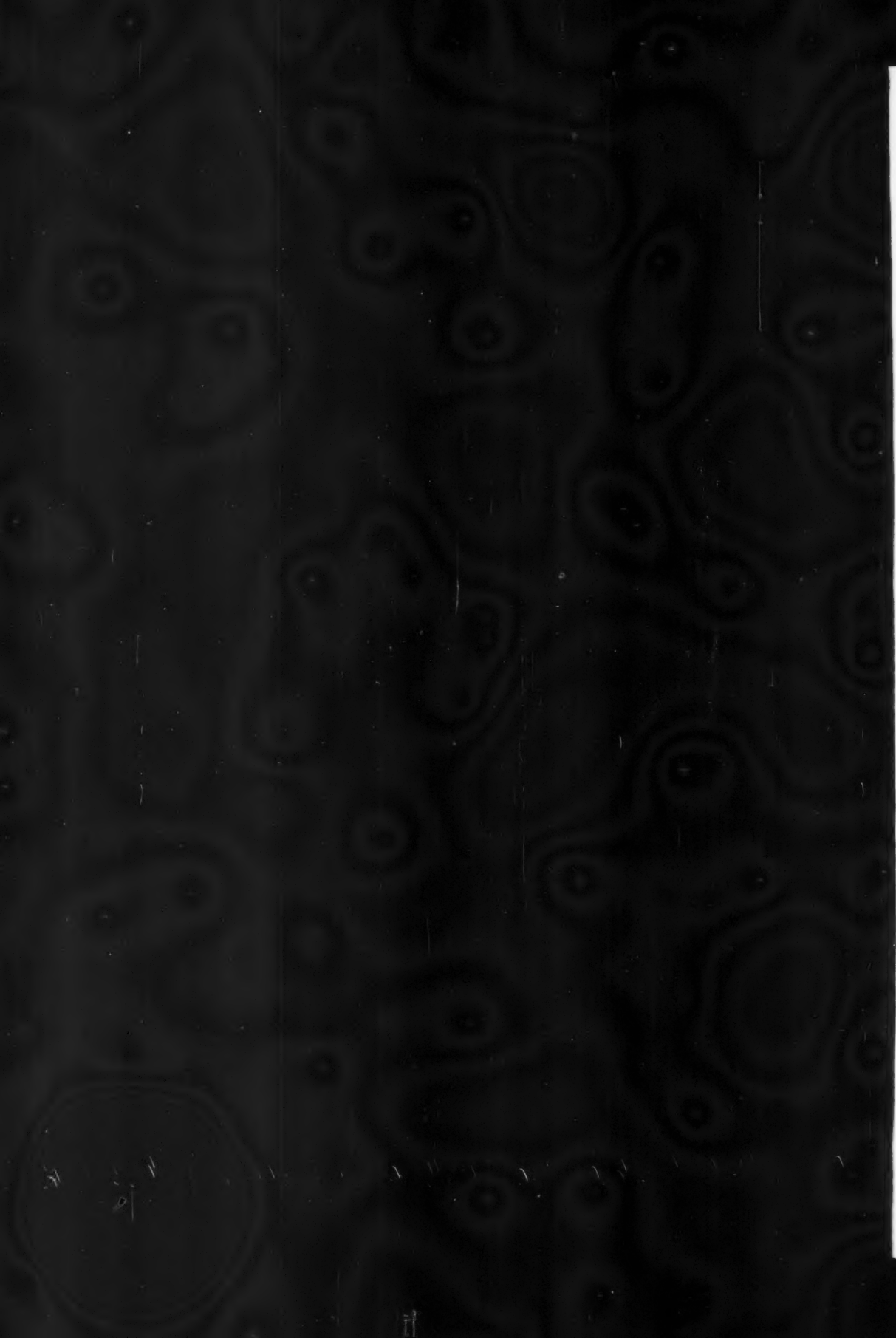

THE MECHANISM OF SUDDEN DEATH IN DISSECTING ANEURYSM WITH INTRACARDIAC RUPTURE

BY

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Received January 20, 1953

A number of observations on cardiac death have been reported (Stroud and Feil, 1948) in man as well as in the experimental animal. However, as stated recently by P. D. White (1951), " We need more." A case is presented in which a dissecting aneurysm of the aorta caused sudden death by perforation into cardiac structures. Close electrocardiographic observation of the terminal events was possible and revealed some unusual features. While probably related in part to the particular type of death, these observations may provide some insight into the variety of phenomena associated with the termination of cardiac activity and of human life.

Case Report

M.A., a 74-year-old white man, was found at noon in his home in deep coma, cyanotic, with laboured respiration, and a slow pulse. According to the reports of the family he was not previously ill, his only complaints being weakness. On arrival at the hospital he was awake, responded to pain stimuli but not to questions. His colour was normal, the pulse rate 46 a minute, the respiration 30, the blood pressure 140/80 mm. Hg. The heart sounds were slow and regular and variations of the intensity of the first sound were noted. Subsequently the pulse rate changed to 75 regular, the blood pressure to 190/100 and the respiration to 22 a minute.

Physical examination showed normal reaction of the pupils to light, and on fundoscopy, flat discs, congestion of the vessels, and no hæmorrhage nor exudates. Some nuchal rigidity was present. The lungs were normal to percussion and auscultation. The heart appeared of normal size on percussion, its action was regular, and no murmurs were heard. The liver and spleen were not enlarged. The neurological findings were normal except for hyperexcitability of the deep tendon reflexes: no abnormal reflexes could be elicited.

The patient continued to improve for the next two hours. His sensorium became clear but he still answered question in a peculiar fashion. At 8 p.m. he was able to give a detailed history which revealed little more than some abdominal distress during the last months: it was described as being diffuse in nature and not associated with nausea, vomiting, or bowel distress.

During the following day the patient remained well and his condition was unchanged. The temperature varied between 97° and 99° F; respiration between 18 and 20, and heart rate between 68 and 80. The urine had a specific gravity of 1022 and showed some albumin, the sediment showed hyaline and granular casts and occasional red cells. Fasting blood sugar was 119 mg. and blood urea nitrogen 17·6 mg. each per 100 ml.; the Kahn test was negative. Hæmoglobin was 14·6 g., red blood count 4·8 million, white blood count 9200 with a normal differential count. The sedimentation rate was 19 (Wintrobe). For technical reasons no electrocardiograms could be obtained on the first two days. The clinical diagnosis at this time was cerebral arteriosclerosis and cerebral ischæmia due to Stokes-Adams syndrome.

On the third morning the first electrocardiogram was taken. While lead I was being recorded (Fig. 1a) he suddenly stopped breathing and became cyanotic. The pulse became imperceptible and the blood pressure dropped to zero. The heart sounds became slow and irregular and within a few minutes stopped completely. Emergency treatment (consisting of artificial respiration, pressure oxygen, infusion of plasma and adrenaline) was unsuccessful and clinical death took place within a few minutes. However, signs of electrical activity of the heart were recorded for forty more minutes. Pertinent and successive parts of cardiograms obtained during this period are reproduced in Fig. 1 and 2 and their interpretation is given in the respective legends.

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Necropsy was performed the same day by Dr. O. Saphir and Dr. B. Taylor to whom we are indebted for the following description of anatomical findings and Fig. 3. The pathological diagnosis was idiopathic cystic necrosis of the media of the aorta; dissecting aneurysm of the ascending aorta with extension to the arch, the innominate, right and left common carotid arteries and to the right atrium; perforation into the pericardium with hæmopericardium; generalized arteriosclerosis; acute passive hyperæmia of the liver, spleen and kidneys; anomalous origin of the left posterior cerebral artery; arterio- and arteriolo-nephrosclerosis.

The significant findings were localized to the heart and the great vessels. The pericardial cavity was distended by a mass of freshly clotted blood which enveloped the heart in a layer of 2·5 cm. thickness. It measured about 750 ml. in volume and was easily removed leaving a glistening serous pericardium. The source of the bleeding into the pericardium was localized as an irregular 2 cm. long rent over the right lateral aspect of the base of the aorta at its emergence from the left ventricle. The tear opened into the transverse sinus of the pericardium and was surrounded by a 3 cm. wide subserosal ecchymosis.

The heart weighed 410 g., being moderately hypertrophied primarily due to thickening of the left ventricular myocardium which measured up to 17 mm. in width. The endocardium was smooth and transparent throughout and the circumference of the valvular orifices well within normal limits. The cusps were thin and pliable, showing no evidence of inflammatory or degenerative distortion.

The aortic intima exhibited moderate atheromatosis but there was no calcification or ulceration. On the posterior aspect of the aortic arch, 1·5 cm. above the aortic ring, there was an irregular sinuous tear of the intima which ran obliquely upwards for a distance of 3 cm. and extended outwards into the intima. The edges of the rent were separated by a fresh blood clot which led into a medial dissection. This completely encircled the aorta thickening the wall to 3 or 4 cm. Proximally, it extended into the root of the aorta surrounding the orifice of the coronary artery, but neither ostia nor lumina of the coronary arteries were occluded. In addition, the hæmorrhage could be traced into the right atrium where it formed an extensive subendocardial hæmorrhage of the right surface of the inter-auricular septum. Measuring 4·5 cm. in diameter, this hæmatoma reached the medial leaflet of the tricuspid valve, thus involving the region of the A-V node (Fig. 3). Distally the medial dissection progressed to the origin of the left common carotid artery continuing into the media of the innominate and right and left carotid arteries for a distance of about 4 to 5 cm. On transection of the vessels, however, their lumina were not appreciably narrowed.

Microscopic sections of the aorta distal to the dissection contained foci of mucinous degeneration consisting of a deposition of interstitial basophilic material. In areas this coalesced to form irregular cystic spaces of various sizes filled with myxomatous material. Sections through the hæmorrhage localized it to the middle and outer thirds of the media. There was neither an exudative nor proliferative response. The intimal changes were of the usual atheromatous nature consisting of fibrous thickening in which were found cholesterol slits and lipid laden histiocytes.

Comment

A correlation of clinical, anatomical, and electrocardiographic data suggests the following reconstructions of events leading to sudden death in this patient. Dissection of the aortic wall, which was the seat of a typical idiopathic medial necrosis probably took place in two separate episodes. At first, dissection beginning at the site of the intimal tear near the aortic root was carried in a distal direction and produced the comatous state for which the patient was admitted to the hospital. Cerebral symptoms like disorientation, syncope, and coma are known to occur as initial signs of aortic dissection (3); in association with bradycardia this has been ascribed to involvement of the endings of the depressor nerves (4). Since in this instance, hæmorrhage extended into the walls of both carotid arteries, a resulting cerebral ischæmia (5) might also account for the initial symptoms. The dissection then apparently stopped at this level and the patient recovered. However, 36 hours later when the patient was moved in order to obtain a cardiogram, a second and fatal dissection took place, this time directed towards the root of the aorta. The sequence of observed cardiographic events (Fig. 1 and 2) suggests that hæmorrhage into the atrial septum shortly preceded the terminal perforation into the pericardial cavity.

While rupture into the pericardium and death from cardiac tamponade is seen commonly subsequent to extension of an aortic dissection in a proximal direction (5–8) only a few instances are on record where hæmorrhage took place into cardiac structures surrounding the aortic root (5, 9–11). In two of the reported cases (5, 11) the post-mortem findings were similar to those in our case in that a resulting hæmatoma of the atrial septum closely approached the region of the A-V node (Fig. 3). These patients also had marked bradycardia at the time of the dissection and,

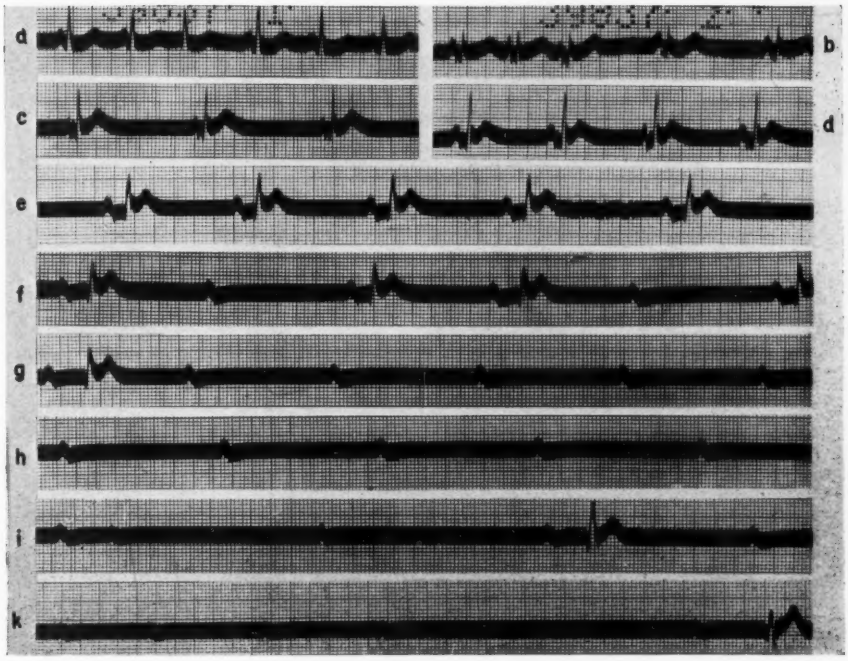

FIG. 1.—Part of successive cardiograms recorded during and following clinical death. (Strip a is lead I, all others, lead II.) The terminal stages of auricular activity and of A-V conduction are seen.

(a) *Alterations of auricular conduction.* Auricular rate regular at 96 a minute, but alterations in contour of P. P–R interval between 0·12 and 0·14 sec. The third ventricular complex is premature and originates in the A-V node.

(b) *Depression of auricular conduction and S-A block.* Auricular rate changes abruptly from 103 to 52, P varies in size and contour, P–R interval unchanged (0·14 sec.).

(c) *Ectopic auricular pacemaker.* Rate regular and slow (48), P bizarre in contour, P–R interval 0·10 sec. Increased size of QRS and elevation and shortening of ST–T.

(d) and (e) *Periods of auricular irritation with runs of auricular tachycardia.* In (d) the auricular rate is faster (68), P remains notched and diphasic, P–R 0·16 sec. Occasionally P waves more bizarre and P–R interval shortened, as in preceding strip. In (e) auricular rate slowed to 46, P diphasic and widened, and P–R interval slightly prolonged (0·20 to 0·24 sec.) A short run of four premature auricular complexes at an irregular rate of about 206, differing in contour from other P waves in this strip, is seen following the fourth ventricular complex; none of these are conducted to the ventricles.

(f) *Development of A-V block.* Large and diphasic P waves occur at a slow (48) and uneven rate. A-V block with Wenckebach phenomenon at a 3:2 ratio, P–R increasing from 0·24 to 0·32 sec. As in strip (e), the S–T segment is elevated indicating alteration of ventricular deactivation.

(g) to (k) *Progression to complete A-V block with transient depression of primary and secondary pacemakers.* Auricular rate slows further to 37 and ventricular complexes disappear (g to h). A-V conduction after (h) completely interrupted. Occasional idioventricular beats in (i) and (k), P waves irregular. The diminishing rate and size of P and alterations in contour indicate progressive deterioration of formation and spread of auricular impulses.

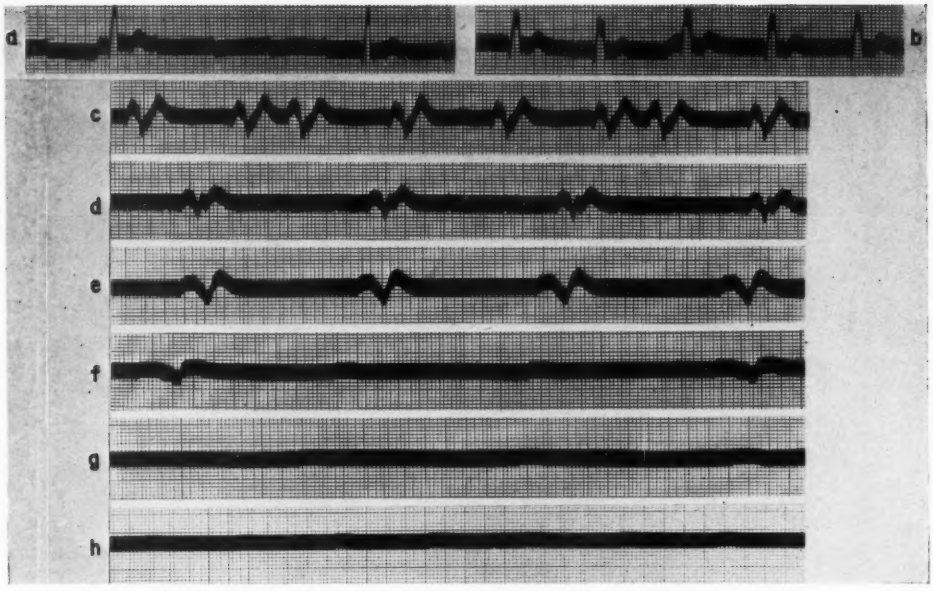

FIG. 2.—Strips (a) to (h) are the continuation of Fig. 1 and portions of successive longer tracings, recorded in lead II. The death of the auricles and ventricles is revealed in these tracings.

(a) to (d) *Disappearance of auricular activity, irregular idioventricular pacemaker, development of intraventricular* block. The last manifestations of auricular activity occur intermittently (a, b, and d) at a relatively rapid rate of 103, Before disappearing, P becomes more and more shallow. There is complete A-V block, with an idioventricular pacemaker at varying rates. Although in (a) and (b) the QRS complex widens progressively (0·12 to 0·16), its contour remains similar to conducted beats in Fig. 1. Thus, the impulse seems to originate somewhere above the bifurcation of the common bundle but is transmitted to the ventricles with progressive impairment of intraventricular conduction. The long ventricular interval in (a) is a multiple of the short ones seen in (b); hence, the derangement of intraventricular conduction appears to result, at times, in complete " exit block " of the pacemaker. (Compare with similar events in the auricles seen in Fig. 1b.) Following an allorhythmic phase with intermittent bigeminal rhythm (c), the ventricular action becomes slow and almost regular, but impairment of intraventricular conduction progresses further. Thus, in (c) and (d), the QRS complex is lower, widened to 0·24 sec., and consists of two distinctly separated diphasic portions. T waves upright as before.

(e) to (h) *Progression of intraventricular block to dissociation of ventricular activation and ventricular arrest.* No sign of auricular activity. Ventricular rate further slowed to 32. Separation of ventricular activation into two portions now more marked, resulting in two negative initial deflections, each of which merges into its own positive final deflection. In (e), the interval from the beginning of the first to the end of the second QRS portion measures 0·36 sec. Ventricular complexes of the same type, but lower in amplitude and even longer in duration (0·42 sec.) are seen at the beginning and at the end of (f); in its middle part only the initial portion with its T wave occurs at the expected time. Thus, at this stage, intraventricular conduction seems so deranged that the idioventricular impulse activates one part of the ventricles but temporarily fails to reach the other. This ventricular block becomes complete in (g), where only low and regular deflections are seen corresponding to the initial parts of ventricular complexes of the preceding strips. Finally, in (h), only traces of activity of one part of the ventricle represent the last recorded electrical events.

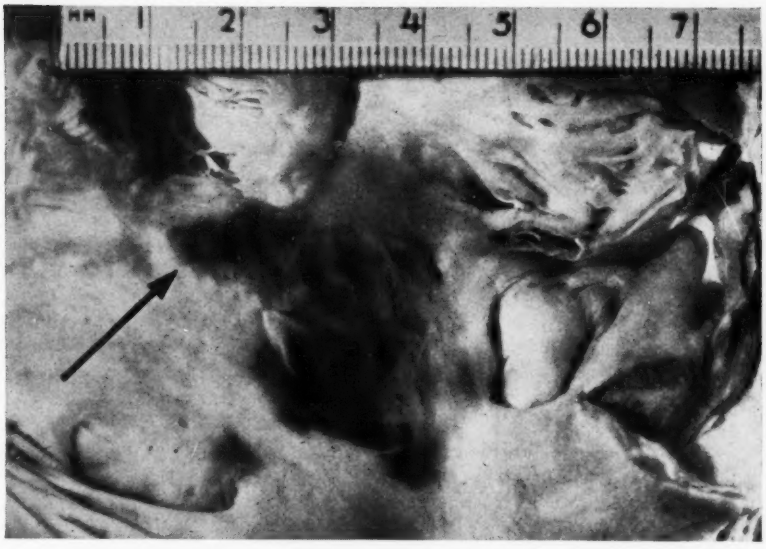

FIG. 3.—View into the cavity of the right atrium revealing the extensive subendocardial hæmorrhage in the atrial septum, extending to the region of the A-V node (at arrow).

although no electrocardiograms were obtained, this was related to the autopsy findings by one of the authors (11).

While respiration ceased immediately and clinical death took place within a few minutes, signs of electrical activity of the heart continued for forty minutes. Electrocardiograms have been recorded for much longer periods after cessation of cardiac contractions (12). Cardiographic death was then seen to occur in a certain order and in three main stages (13–16). An initial phase of sinus slowing may alternate with rapid phases of auricular activation; in a following phase, auricular activity ceases and ventricular activation is effected by a subsidiary pacemaker; finally there is ventricular arrest which may or may not be preceded by a period of ventricular fibrillation. The question of incidence of terminal ventricular fibrillation has been investigated both experimentally and clinically. Harris (17) who studied cardiac death under various controlled experimental conditions saw fibrillation frequently in conditions favourable for the production of ectopic impulses, e.g. localized ischæmia following occlusion of a coronary artery, while in conditions leading to generalized anoxia and tissue death ventricular arrest was effected by failure of pacemakers or of A-V conduction. In the dying human heart ventricular fibrillation was observed as frequently as simple standstill (1) regardless of the presence or absence of heart disease causing death. To our knowledge no clinical or experimental electrocardiographic observation has been reported describing the mechanism of sudden death from acute cardiac tamponade which undoubtedly was the cause of death in the presented case. Usually, in this condition, death is not instantaneous (18).

Although in general following the pattern outlined above, the electrocardiographic evolution here appeared to be modified, at least initially, and could be related to the particular findings post mortem. Blockage of impulse transmission, first within the auricles and later at the A-V junction appeared to be dominating and was mainly responsible for the slowing, and the initial irregularities of the cardiac action (Fig. 1). A-V block has been considered by some (12) to be rare among the phenomena of cardiac death, but P–R prolongation as well as S-A block has been noted by others (15, 16, 20–22). However, none of their illustrations shows systematic progression to the highest degrees of block such as are seen in Fig. 1. Dissociation of auricular and ventricular action appeared to result from extreme slowing of the primary impulse formation under vagal influences

associated with death (23), rather than from block of A-V conduction. Thus, in all likelihood, the organic lesion in the atrial septum developing in the course of aortic dissection was, by extending to the region of the conduction system, responsible for the cardiographic alterations in the first part of this observation.

As a result of complete interruption of A-V conduction, a period of complete ventricular standstill is seen in Fig. 1h followed by the appearance of an idioventricular pacemaker of supraventricular origin, discharging initially at an extremely slow and irregular rate. Signs of severe depression of ventricular pacemakers varying with those of irritation of these pacemakers are common phenomena associated with cardiac death (16). How far the administration of stimulating drugs like adrenaline, during the last efforts to restore life, might be responsible for irregularities of the terminal cardiac activity in this and in previously reported cases is impossible to assert. However, if the interpretation of the tracings taken during the second part of observation (Fig. 2) is correct, the profound ventricular arrhythmias were in this instance not so much the result of terminal disturbance of impulse formation of the cardiac impulse but of disturbances in their propagation through the ventricles. First signalled by prolongation of QRS duration (Fig. 2b) the disturbance of intraventricular conduction is seen to develop further in several stages. A temporary block surrounding the pacemaker is suggested by the phenomenon of " exit block " in Fig. 2a. Later, while impulse formation continues at a slow but fairly regular rate, progressive slowing of its propagation through the ventricles can be followed throughout the tracings (Fig. 2d–e) resulting in separation of activation and deactivation of the ventricles into two distinct portions; then the impulse apparently failed, first temporarily and eventually permanently (Fig. 2f–g), to activate a major part of the ventricles, before these last manifestations of electrical activity also disappeared.

Ever since investigations were made into the mysteries of cardiac death interest has centered mainly around two points: What is the last part of the heart to die, the ultimum moriens? And what are the last signs and mechanisms of its activity? Shallow terminal waves of the type seen in Fig. 2g–h may be interpreted as representing terminal auricular activity unless their development can be followed in long successive strips. The analysis of the tracings in Fig. 2 leaves little doubt that, in accordance with the majority of observations (13, 14, 16, 21, 23–26) and in contrast to some others (22, 27–29), the last part of the heart to cease to function was the ventricles.

These last moments of ventricular activity have been described as giving rise to characteristic " agonal ventricular complexes " (30) consisting of large monophasic potentials of prolonged duration with elevation of S–T and fusion of QRS and T. The mechanism responsible for this bizarre contour has never been established. Whatever the immediate cause may be (whether injury currents due to terminal hypoxia, alterations of intracellular or extracellular potassium in the myocardium as recently suggested (31), or other metabolic disorders so far undetected), the tracings that form the basis of this report suggest that one of the operating mechanisms may be a profound disturbance of cardiac conductivity. Whether this is related to the acute changes of cardiodynamics and the circulatory failure effected by the sudden cardiac tamponade (32, 33) remains a matter of speculation that warrants further study.

Summary

In a case of dissecting aneurysm of the aorta extension to the aortic root resulted in hæmorrhage into the atrial septum involving the region of the A-V node, and eventually lead to a fatal rupture into the pericardium and sudden death.

Electrical activity of the heart persisted and was recorded for forty minutes after clinical death. A detailed analysis of the records suggested that the dominant factor in the production of terminal irregularities of the heart action was a profound and progressive disturbance of cardiac conductivity involving successively the auricles, A-V conduction, and intraventricular conduction. Cardiac arrest occurred following a period of dissociation of ventricular activation due to the development of ventricular block. A possible relationship of the unusual anatomical and electrocardiographic findings is considered.

We wish to express our appreciation to Dr. L. N. Katz for his valuable suggestions, and to Dr. Robert Stern for his permission to report observations made on his patient. We are grateful for aid from the J.N. and A.D. Nast Fund for Cardiovascular Research and the Michael Reese Research Foundation.

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OBSERVATIONS RELATING TO THE ÆTIOLOGY OF PATENT DUCTUS ARTERIOSUS

BY

R. G. RECORD AND THOMAS McKEOWN

From the Department of Social Medicine, University of Birmingham

Received June 25, 1953

In a recent investigation of 633 cases of congenital heart disease it was noted that the incidence of patent ductus arteriosus appeared to be higher in first-born than in later-born (MacMahon, 1952). The number of affected (48) was rather small, however, and it seemed important to confirm the observation on a larger series. In the present communication data are recorded on 166 cases of patent ductus arteriosus; it is shown that affected boys are more common among first-born than among later-born, and affected girls are more common among children of young mothers than of older mothers. In view of the association of incidence with maternal age and birth order we have looked for other evidence of environmental influence, and it is noted that (*a*) there is a marked seasonal fluctuation in the number of affected girls (but not of boys), and (*b*) a history of fœtal distress at birth was recorded in a considerable proportion of cases. The possible significance of the last observation is discussed in relation to experimental work on the mechanism of closure of the ductus.

Material and Methods

The series of 166 cases was assembled from children born in the Birmingham hospital region in the period 1936 to 1952.

(*a*) Forty-eight cases born to Birmingham mothers in the years 1940–49 and included in the earlier series (MacMahon *et al.*, 1953),

(*b*) Eleven cases born to Birmingham mothers in the years 1940–49, and not included in the earlier series,

(*c*) Fourteen cases born to Birmingham mothers in the years 1936–39 and 1950–52,

(*d*) Forty-eight cases born outside Birmingham in the period 1936–52, but treated in Birmingham hospitals, and

(*e*) Forty-five cases born and treated outside Birmingham.

Excluded from the series (except in Table IV) are 16 infants who died in the neonatal period, for whom the diagnosis was considered unreliable. We have also excluded cases in which there was another defect of the heart or great vessels, on the grounds that persistent patency of the ductus may have been secondary to the other lesion.

Among the 121 cases identified by Birmingham pædiatricians and pathologists [(*a*)–(*d*) above] the diagnosis was confirmed at operation in 79 and at autopsy in 19. In the remaining 23 cases the diagnosis rested on clinical examination and the results of special investigations. Details of the 45 cases born and treated outside Birmingham were provided by pædiatricians practising in the Birmingham region, but did not include the methods by which the diagnosis was established.

Mothers living within 10 miles of Birmingham were visited and a history recorded which included the date of birth of the mother, the date and place of birth and birth rank of the patient, and details of the related pregnancy and labour. The same data were obtained by writing to the 52 mothers living more than 10 miles from Birmingham. For 37 children born in hospital we were able to obtain more reliable information about pregnancy and birth by inspection of the hospital delivery notes.

The examination of maternal age and birth rank relies on a comparison of the affected with the population of births from which they are drawn. The distribution of this population by maternal age and birth rank is estimated from a sample of 1015 Birmingham births (see MacMahon, 1952) and from data for the Region Midland I (1940–49) published in the Registrar-General's Statistical Reviews for England and Wales (Part II, civil). The proportion of Birmingham births among affected is 44 per cent, and the Registrar-General's data for the Region have therefore been weighted in relation to the sample to give roughly the same proportion of Birmingham births in the controls.

Incidence Related to Birth Rank and Maternal Age

Table I gives the distribution by birth rank and maternal age of 152 affected (48 males and 104 females), and the percentage distribution of controls. The proportion in the first birth rank is higher for affected (53·9%) than for controls (39·8%) as are also the proportions at low maternal ages. The results are confirmed in Table II, which compares the numbers of cases observed at birth ranks 1 (82) and 2 and over (70), with the numbers expected (61 and 91 respectively) on the assumption that affected are distributed in the same proportions as controls. The same treatment is used in Table III to show that the number of patients born to mothers under 25 (57) is higher than the number expected (42) if incidence were unrelated to maternal age.

TABLE I

152 Cases of Patent Ductus Arteriosus distributed according to Birth Rank and Age of Mother

Maternal age	Birth rank										All birth ranks		Both sexes (percentage)	Controls (percentage)
	1		2		3		4		5 and over					
	M	*F*	*M*	*F*	*M*	*F*	*M*	*F*	*M*	*F*	*M*	*F*		
Under 20 ..	4	3	—	2	—	—	—	—	—	—	4	5	5·9	3·0
20–24	9	27	—	10	1	1	—	—	—	—	10	38	31·6	24·8
25–29	12	14	4	9	—	3	—	1	—	1	16	28	28·9	30·8
30–34	5	4	4	5	2	4	—	2	1	3	12	18	19·7	22·8
35–39	1	1	—	1	2	6	—	3	2	—	5	11	10·5	13·8
40 and over ..	—	2	—	—	—	—	—	1	1	1	1	4	3·3	4·8
All ages ..	31	51	8	27	5	14	—	7	4	5	48	104	—	—
Both sexes ..	53·9%		23·0%		12·5%		4·6%		5·9%		—		100	—
Controls ..	39·8%		29·0%		14·0%		7·4%		9·8%		—		—	100

Because of the high correlation between maternal age and birth rank (r is approximately 0·5) it is desirable to separate the effects of these two variables. The method employed for this purpose is essentially a process of standardization which uses the percentage distribution of controls to give the numbers of affected expected: (*a*) in each birth rank and maternal age group (Tables II and III); (*b*) in each birth rank when the influence of maternal age is removed (Table II); and (*c*) in each maternal age group when the influence of birth rank is removed (Table III). It is shown that the association of incidence with primogeniture is independent of maternal age, but the association with age is negligible when the influence of birth rank is removed.

The same methods are used to examine separately for males and females the association of incidence with the two variables. The proportion of males in the first birth rank is substantially raised, and this result is independent of maternal age (Table II); indeed the incidence of males appears to be unrelated to age (Table III). On the other hand, the incidence of affected females is unrelated to birth rank (Table II), but is raised at maternal ages under 25. A possible, if not a probable, explanation of this sex difference is referred to below under the discussion of sex ratios.

TABLE II

ASSOCIATION OF INCIDENCE WITH BIRTH RANK

	Both sexes		Males		Females	
Birth rank	1	2 and over	1	2 and over	1	2 and over
Observed number	82	70	31	17	51	53
Expected number	60·6	91·4	19·1	28·9	41·4	62·6
χ^2	12·62		12·23		3·67	
p	$<0·01$		$<0·01$		$0·05<p<0·10$	
Expected number (influence of maternal age removed)	68·3	83·7	20·6	27·4	47·7	56·3
χ^2	4·97		9·14		0·42	
p	$0·02<p<0·05$		$<0·01$		$0·5<p<0·7$	

TABLE III

ASSOCIATION OF INCIDENCE WITH AGE OF MOTHER

	Both sexes		Males		Females	
Maternal age	Under 25	25 and over	Under 25	25 and over	Under 25	25 and over
Observed number	57	95	14	34	43	61
Expected number	42·3	109·7	13·4	34·7	28·9	75·1
χ^2	7·09		0·04		9·48	
p	$<0·01$		$0·8<p<0·9$		$<0·01$	
Expected number (influence of birth rank removed)	50·2	101·8	17·4	30·6	32·7	71·3
χ^2	1·39		1·05		4·69	
p	$0·2<p<0·3$		$0·3<p<0·5$		$0·02<p<0·05$	

THE CONDITION OF THE CHILD AT BIRTH

Since we have no reason to suppose that variation associated with maternal age and birth order is determined genetically, the observations recorded above must be attributed to environment. This prompts consideration of the kind of influence that might be expected to be related to the ætiology of patent ductus arteriosus, and to operate more frequently in first-born and at low maternal ages. A possibility that seemed worth exploring was suggested by Kennedy's proposal (1942) that uncomplicated persistent patency of the ductus should not be regarded as a malformation, but should be attributed to defective oxygenation of the blood during birth or shortly after. Since difficulties of labour are undoubtedly more common in first-born, it seemed reasonable to enquire whether there was evidence of fœtal distress during delivery of affected patients.

Place of birth was known in 150 cases. Unfortunately we have been able to examine notes recorded at delivery for only 37 hospital births; in 16 (43%) there was a history of fœtal distress. For the remaining 15 hospital births whose records were lost, and for 98 domiciliary and nursing-home births, we have had to rely on mothers' statements, according to which 4 (27%) and 22 (22%) of the infants in the two groups respectively showed signs of distress at birth. Brief details of the observations accepted as evidence of fœtal distress were given in an appendix, but have been omitted to save space. Shortly, representative notes were as follows: toxæmia and blue asphyxia; long labour and fœtal distress; thirty-six hour labour and pneumonia on the third day; fœtal distress in second stage, cord obstructed and infant very shocked; white asphyxia and much inhaled mucus; blue asphyxia and cord round neck; not expected to live; forceps delivery and pneumonia at two days; and breech delivery and blue at birth.

Although the information taken from hospital notes can be regarded as reliable, it is evident that the mother's knowledge of the circumstances at birth must be interpreted with some reserve. Nevertheless some of the details are of a kind about which it is hard to believe that a mother could be mistaken (administration of oxygen, pneumonia, a child not expected to live),

and having regard for the higher incidence of complications in cases in which notes were inspected, it seems likely that the mother's history understates the frequency of complications. But whether we consider 43 or 28 per cent as the more acceptable figure, it can hardly be doubted that the proportion of infants with a history of distress is very much higher than would be expected among normal births. Lund (1941) noted that the proportion of infants who did not breathe within one minute of birth and cry lustily soon after was 15 per cent; Keith and Norval (1950) gave 5 per cent as the frequency of asphyxia and delayed respiration.

In seeking an explanation for the high incidence of fœtal distress in cases of patent ductus arteriosus, we may examine first the possibility that asphyxia is secondary to the abnormality. Since the ductus normally remains open for the first few minutes of extra-uterine life (Kennedy and Clark, 1941; Barclay *et al.*, 1944; Lind and Wegelius, 1952) this explanation is obviously unacceptable. It also would not account for cyanosis shortly after birth, for in the absence of other cardiovascular defect or obstruction to the circulation in the lungs, the direction of blood flow through the ductus is from left to right. It seems unlikely therefore that these cases of fœtal distress, asphyxia, or cyanosis can be ascribed to patency.

Before considering the possibility that the abnormality may sometimes be secondary to difficulties at birth, it may be helpful to summarize briefly the results of experimental work on the mechanism of closure. At the outset it is necessary to distinguish between functional closure, which is effected rapidly after birth (in man: Keith and Forsyth, 1950; Lind and Wegelius, 1952; in the guinea-pig: Kennedy and Clark, 1941; in sheep: Barclay *et al.*, 1944; in dogs, Everett and Johnson, 1951), and anatomical obliteration of the lumen, which may not be complete for some weeks (Christie, 1930; Jager and Wollenman, 1942). This distinction was clearly recognized by Gerard (1900), and Wells (1908) stated that functional closure of the ductus " is a physiological process taking place simultaneously and instantaneously in every new-born child, and therefore there must be some mechanism which can be relied upon always to perform this occlusion. Any explanation that involves connective tissue proliferation must be inadequate, for the duct is patent and then is at once occluded when the child begins to breathe; it is necessary to distinguish between the instantaneous occlusion of the duct and its subsequent obliteration."

Hamilton *et al.* (1937) showed that in dog and rabbit fœtuses inspiration lowered the pressure in the right ventricle, and they considered that in these species the tendency to reversal of blood flow through the ductus is prevented by a flap-like valve at the aortic end. There is no structure of this type in the human fœtus, and Barclay *et al.* (1944) found no evidence of a valve in the guinea-pig, or in a moribund lamb examined by cineradiography.

Perhaps the most significant observations in the present context are those of Kennedy and Clark (1942) on the guinea-pig. They noted that artificial ventilation of the lungs with nitrogen did not cause closure; but ventilation with an oxygen-containing mixture, or intravenous injection of oxygen, was followed rapidly by closure of the ductus, and this result was repeated after section of all known nervous connections to the heart. They concluded that under normal physiological conditions respiration is the most important stimulus to closure.

Barron (1944) was unable wholly to accept this chemical explanation of the mechanism, and drew attention to the fact that the ductus remains open during fœtal life, although the percentage of saturation of oxygen in the blood may be high: " In utero the ductus is open, and it certainly is closed in lambs before the oxygen content of their blood returns to the intra-uterine level." But data published by Barcroft *et al.* (1940*a*) do not support this view: in sheep the oxygen saturation of carotid blood varied between 37 and 52 per cent during the last week of gestation, and rose within a few minutes after birth (Barcroft *et al.* 1939). The high values referred to by Barron were recorded by Barcroft *et al.* (1940*b*) some weeks before term, and it may be questioned whether it is reasonable to base an opinion about the mechanism of closure after birth on observations at this time. Barron's own report (1944) that perfusion of the fœtal lamb with oxygen saturated blood did not lead to closure is hardly convincing, since formalin injected to fix the tissues may have caused relaxation of the ductus—a point made in another context by Barcroft (1946).

A more serious objection to the chemical explanation of the mechanism is provided by a single case recorded by Ardran *et al.* (1952) who used cine-angiography to demonstrate constriction of the duct after 21 seconds, and closure after a further 64 seconds and before ventilation of the lungs, in a lamb whose umbilical cord had been tied. On the other hand Ekström (1952) reported that Johnsson had shown by angiocardiography a widely patent ductus with right to left circulation in a cyanosed new-born infant: a

week later when the cyanosis had disappeared the ductus was found to be closed. Lind and Wegelius (1952) also used angiocardiography to show patency of the ductus with right to left blood-flow in two asphyxiated new-born infants.

There is thus a good deal of evidence that asphyxia at birth may delay closure of the ductus. But it is not easy to see why persistent patency should result from a condition that is apparently so transient. We can offer no explanation, although we may note that the respiratory embarrassment of the fœtus may not always be so transient as it appears. Intra-uterine anoxia may stimulate the fœtus, and cause it to inspire amniotic fluid containing epithelial cells and vernix which become trapped in the alveolar ducts (Wilson and Farber, 1933; Potter, 1952). Farber and Sweet (1931) found large quantities of cornified cells and vernix in the lungs of 15 per cent of infants who died between two hours and five weeks after birth. This suggests that the results of severe pre-natal anoxia may affect the lungs for a protracted period until the vernix has been absorbed; respiratory exchange may be limited further by the presence of micro-organisms. In this context it is interesting to note that of the 44 cases of fœtal distress listed in the appendix, one had bronchitis at birth, and three others had pneumonia at the second or third day. These observations merely remind us that respiratory embarrassment may commonly last for days rather than minutes; they do not dispose of the objection that closure might be expected to follow relief of the embarrassment unless the possibility of closure is limited to a short period after birth. So far as we are aware there is no direct evidence on this point. It has been shown in Fallot's tetralogy that even in the presence of anoxia the ductus may be obliterated many months after birth, but it is not certain that this observation has much bearing on the normal mechanism of closure.

Seasonal Incidence

Rutstein *et al.* (1952) examined the seasonal incidence of 254 cases of patent ductus arteriosus in Massachusetts, and found a low incidence from February to August, and a high incidence from October to January. We have compared the monthly distribution of these cases with that of 162 affected from the Birmingham region. (We are able to compare the actual numbers, because there are only small seasonal fluctuations in the numbers of related births.) The two distributions are quite different, incidence in Birmingham being highest from May to December and lowest from January to April.

An interesting feature of the seasonal incidence is exhibited by separate examination of the two sexes (Fig. 1). With the exception of a small increase during November and December, the number

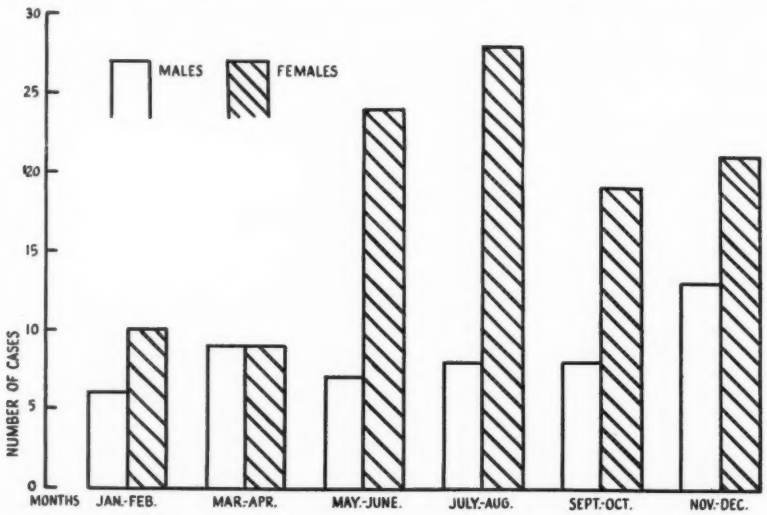

Fig. 1.—Seasonal incidence of the time of birth of patients with patent ductus arteriosus.

of affected males is fairly constant throughout the year. The seasonal variation is due to a marked seasonal fluctuation in the number of females, which is only slightly greater than that of males during the first four months of the year, but rises greatly during the summer months (May to August) and remains relatively high during the rest of the year. This results, as would be expected, in marked seasonal variation in the sex ratio of affected: the proportion of males fluctuates between 22 (July–August) and 50 per cent (March–April).

Rutstein *et al.* (1952) showed that the seasonal incidence of their cases corresponded roughly with that of rubella notifications in Massachusetts seven months earlier. Fig. 2 shows a similar comparison between Birmingham cases of patent ductus arteriosus and rubella notifications in Manchester (1936–51: war years excluded). Rubella is not notified in Birmingham, but it seems unlikely that its seasonal incidence would differ appreciably from that in Manchester, an industrial city of approximately the same size less than 100 miles away. The two distributions are entirely different and give no grounds for the view that the seasonal fluctuation in the number of affected could be attributed to rubella.

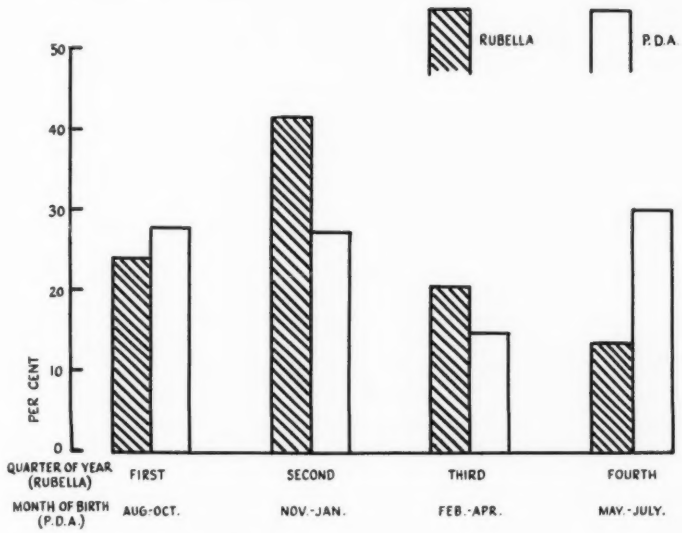

FIG. 2.—Seasonal incidence of patent ductus arteriosus (Birmingham Region, 1936–52 compared with rubella notifications in Manchester (1936–51).

A reasonably satisfactory history of the pregnancy was obtained for 150 cases, which included three with abnormalities involving the special senses (blindness in one, and deafness in two). A history of rubella during the first three months of pregnancy was elicited in two of these three cases, and in only one of the remaining 147 cases. Although the results of retrospective enquiry on a matter of this kind must be treated with reserve, the difference between the two groups is impressive: it gives some grounds for the belief that (*a*) a history of rubella can often be elicited if it is present, and (*b*) rubella is not commonly related to the ætiology of patent ductus (a conclusion in accord with results published by Dogramaci and Green, 1947, and Lynxwiler and Wells, 1950), unless the defect is associated with other abnormalities. It is possible that by confining attention to cases uncomplicated by other cardiovascular defects we have reduced the apparent significance of rubella, since Gibson and Lewis (1952) suggested that a history of rubella is relatively more common in cases of patent ductus arteriosus associated with other heart lesions.

Sex Ratio

It is generally believed that the sex ratio in patent ductus arteriosus (expressed as the percentage of males among affected) is about 30 per cent (Abbott, 1936; Gilchrist, 1945; Brown, 1950). Of the 166 cases included in the present series, 51 (30·7%) were males. We have, however, excluded 16 neonatal deaths, and when these are included the sex ratio is a little higher (34%).

Table IV shows that the proportion of affected which are males is related to the time at which cases are observed, being 29 per cent in patients alive at one year, 44 per cent in patients who died between 1 and 12 months, and 62 per cent in neonatal deaths. The same association between sex ratio and the age of patients on whom the observations are made is also evident in 244 reported

TABLE IV

Sex Ratio according to Age

Birmingham region	Males	Females	Percentage of male
Neonatal deaths	10	6	62
Later infant deaths ..	8	10	44
Cases alive at 1 year ..	43	105	29
Total	61	121	34
Cases reported *			
Under 1 year	7	3	70
1–4 years	16	25	39
5 years and over	61	132	32
Total	84	160	34

* Derived from 14 papers (indicated in the list of references by asterisks).

cases (Table IV). It is clear therefore that the proportion of males among all children affected is higher than most estimates suggest, and if the number of undiagnosed early deaths is relatively large, it is not impossible that numbers of the two sexes affected at birth are nearly equal.

The higher early mortality in males suggests a possible, though perhaps not a probable explanation of the difference between males and females in the association of incidence with maternal age and birth order (Tables II and III). This difference is exhibited in another way in Table V. The percentage of males is highest (46%) in first children of women aged 25 and over, and lowest (7%) in later children of women under 25. These differences suggest the possibility that the proportion of males among cases of patent ductus arteriosus is related to social circumstances, since first births at high maternal ages, and later births at low maternal ages, are characteristic of favourable and unfavourable social circumstances respectively. This point is demonstrated in Table VI, in which Scottish data are used to give the proportion of births in social classes

TABLE V

Sex Ratios according to Birth Rank

Maternal age		Birth rank		
		1	2	3 and over
Under 25	Males	13	1	
	Females	30	13	
	Percentage of males	30	7	
25 and over	Males	18	8	8
	Females	21	15	25
	Percentage of males	46	35	24

I and II (the most favourably placed) according to birth rank and maternal age. Since early mortality is higher in males than in females, it is conceivable that the association between sex and maternal age and birth order in patent ductus arteriosus might be explained by assuming that mortality is related to social circumstances, by no means an unreasonable assumption. In this case a lower mortality in males (and hence a higher percentage of males among surviving cases) would be expected in first births at high maternal ages, and a higher male mortality (and a lower percentage of surviving males) in later births at low ages. Whatever the degree of credibility which this explanation merits, it at least reminds us of the kind of interpretation we should have in mind when considering the association of incidence with maternal age and birth rank.

TABLE VI

DISTRIBUTION OF BIRTHS (LIVE AND STILL-BORN) ACCORDING TO SOCIAL CLASS OF FATHER. (SCOTLAND, 1950)

Maternal age	Social class	Birth rate			Total
		1	2	3 and over	
Under 25	(*a*) I and II	1,520	531	144	2,195
	(*b*) III, IV and V	15,041	6,868	2,806	24,715
	(*a*) as percentage of (*a*)+(*b*)	9·2	7·2	4·9	8·2
25 and over	(*a*) I and II	3,572	3,796	3,631	10,999
	(*b*) III, IV and V	11,878	14,493	25,600	51,971
	(*a*) as percentage of (*a*)+(*b*)	23·1	20·8	12·4	17·5

Derived from data in the Annual Report of the Registrar-General for Scotland, 1950.

FAMILIAL INCIDENCE

(*a*) *Sibs.* A reasonably satisfactory family history was obtained for 150 fraternities containing propositi with patent ductus arteriosus; Table VII gives details of the 7 fraternities in each of which another sib was said to have some form of congenital heart disease. The diagnosis was confirmed at operation or autopsy in 4 of the 7 sibs; in only one fraternity is it certain that the second child also had patent ductus arteriosus.

The incidence of malformation in sibs born before propositi is of little interest (because they are unrepresentative), and we confine attention to 124 live-born sibs born after propositi, of which 3 certainly had congenital heart disease, and one was possibly affected. The corresponding figures for incidence in later sibs (per 1000) are therefore 24 and 32 respectively, appreciably higher than the incidence in the general population of births (3·2 per 1000), but perhaps not significantly higher than in sibs of children exhibiting all types of congenital heart malformation (18 per 1000: McKeown, MacMahon and Parsons, 1953).

Examination of the literature since 1930 gave details of 11 fraternities with two or more cases of patent ductus arteriosus in which the diagnosis appeared to be reliable (Ellis, 1932; Snelling, 1937; Brown, 1939; Stein and Barber, 1945; Kjaergaard, 1946; and Ekström (6 examples), 1952). By including our own fraternity we have obtained information about the sex of 26 patients in fraternities with at least 2 members affected: 3 are males, and 23 females. It can readily be shown that this unusual sex ratio is unlikely to have arisen by chance.

Assuming a sex ratio of 30 per cent male, and considering families containing two affected individuals, the chance of both patients being female is $(0{\cdot}7)^2$ or roughly $\frac{1}{2}$. The chance that in 10 such fraternities both affected will be female in at least 7 is given by summing the first four terms of the expansion of the binomial $(\frac{1}{2}+\frac{1}{2})^{10}$, which gives a probability of 0·172. Considering families containing three affected individuals, the chance of all three being female is $(0{\cdot}7)^3$, and the chance that two such fraternities will each contain females is therefore $[0{\cdot}7^3]^2$ or 0·118. The combined chance of all the affected being female in at least 7 of 10 fraternities containing two patients and in two fraternities containing three patients is $0{\cdot}172 \times 0{\cdot}118$ or 0·02. The observed sex ratio in sibships with more than one affected is therefore unlikely to have arisen by chance,

TABLE VII

DETAILS OF 7 FRATERNITIES IN WHICH A SIB HAD CONGENITAL HEART DISEASE

Birth rank	Sex	Fate	Diagnosis
1	F	Alive at 23 years	
2	M	Alive at 21 years	Congenital heart disease—type not certainly known but not patent ductus arteriosus (clinical examination)
3	F*	Alive at 16 years	Patent ductus arteriosus (operation)
4	F	Alive at 9 years	
1	M	Alive at 19 years	Patent ductus arteriosus (operation)
2	M	Alive at 16 years	
3	M	Alive at 9 years	
4	F*	Alive at 4 years	Patent ductus arteriosus (operation)
5	F	Alive at 7 months	
1	M*	Alive at 14 years	Patent ductus arteriosus (operation)
2	F	Alive at 10 years	Pulmonary stenosis (operation)
1	F*	Died aged 7 weeks	Patent ductus arteriosus (P.M.)
2	F	Alive at 8 years	
3	F	Alive at 7 years	
4	M	Alive at 6 years	
5	M	Alive at 4 years	
6	F	Died aged 3 months	Unspecified cardiac defect (clinical examination)
7	F	Died aged 2 days	Cause of death unknown
8	F	Alive at 5 weeks	
1	F	Died at 3 weeks	Unspecified cardiac defect (clinical examination)
2	F*	Alive at 4 years	Patent ductus arteriosus (clinical examination)
1	M*	Alive at 8 years	Patent ductus arteriosus (clinical examination)
2	F	Died aged a few hours	Transposition of great vessels and ventricular septal defect (P.M.)
	F	Alive at 6 years	
3	M	Alive at 1 year	
1	F*	Alive at 6 years	Patent ductus arteriosus (operation)
2	M	Alive at 4 years	
3	F	Alive at 3 years	
3	F	Alive at 2 years	
5	F	Died aged 3 days	Single ventricle with truncus arteriosus (P.M.)

* Propositus.

and suggests the possibility that cases of patent ductus arteriosus recurring in families may differ ætiologically from other cases. Ekström (1952) made the interesting observation that in patients with affected sibs the ductus is shorter and wider than usual.

(*b*) *Parents.* Until recently, ascertainment of cases of patent ductus arteriosus was very incomplete, and hence a reliable estimate of incidence in parents cannot be given. In the present series one parent (the mother of a male propositus) was affected; the diagnosis was confirmed at operation. Lamy and Schweisguth (1950) refer to a mother with ventricular septal defect and patent ductus arteriosus, whose daughter also had a patent ductus, and Taussig (1947) reported the condition in a father with two affected children and one affected grandchild. The mother of a case recorded by Starer (1953) was also said to be affected. But so far as we are aware there is only one reported instance in which the diagnosis was confirmed in both parent and child (Walker, 1951).

(*c*) *Twins.* One propositus had a still-born twin who was not examined at autopsy; another propositus had a twin of like sex (female) believed to have congenital heart disease, but the child died at 7 months and the diagnosis was not confirmed. Six cases in so-called identical twins have been reported: in two, both members were affected (Smith, 1929; Starer, 1953); in four, only one was affected (McClintock, 1945; Porter, 1947; Wade, 1952; Starer, 1953). Only Wade used special methods to establish the monozygosity of the twin pair.

Summary

Data are recorded in 166 cases of patent ductus arteriosus identified in the Birmingham Hospital Region during the period 1936–52.

Information about the population of births from which cases were drawn is used to show that (*a*) the incidence of affected boys is substantially higher among first-born than among later-born, and this result is independent of maternal age, and (*b*) the incidence of affected girls is unrelated to birth rank, but is raised in children of mothers under 25.

Place of birth was known in 150 cases. Hospital delivery notes were inspected in 37, in 16 (43%) of which there was a history of fœtal distress at birth. For the remaining 15 hospital births whose records were lost, and for 98 domiciliary and nursing-home births, we have had to rely on mothers' statements, according to which 4 (27%) and 22 (22%) of the infants in the two groups respectively showed signs of distress at birth. This incidence is substantially higher than would be expected among normal births, and the possible significance of this observation is discussed against the background of experimental work on closure of the ductus.

The number of affected boys is fairly constant throughout the year, but there is a marked seasonal fluctuation in the number of girls, which is only slightly greater than that of boys during the first four months, but rises sharply during the summer (May to August) and remains relatively high during the rest of the year. Hence the proportion of boys fluctuates between 22 (July–August) and 50 per cent (March–April).

This seasonal incidence of patent ductus arteriosus appears to be unrelated to the incidence of rubella. A history of rubella during the early months of pregnancy was elicited in 2 of 3 cases associated with congenital defects of the special senses (blindness in one and deafness in the other), and in only 1 of 147 uncomplicated cases.

Of the 166 cases 51 (31%) were boys. The proportion of boys among affected is related to the time at which cases are observed, being 29 per cent in patients alive at one year, 44 per cent in patients who died between 1 and 12 months, and 62 per cent in neonatal deaths.

There were 3 confirmed and 1 unconfirmed cases of congenital malformation of the heart among 124 sibs born after propositi. This incidence (24 or 32 per 1000 according as we include 3 or 4 cases) is appreciably higher than the incidence in the general population of births (3·2 per 1000) but is perhaps not significantly higher than in later sibs of children exhibiting all types of cardiac malformation (18 per 1000).

In only one fraternity was a second child as well as the propositus shown to have patent ductus arteriosus. Examination of reported cases gave details of 11 other fraternities with two or more members affected. Of the 26 affected children in these 12 fraternities, 3 were boys and 23 girls.

We are indebted to pædiatricians and pathologists of the Birmingham region, and in particular to Dr. C. G. Parsons and Mr. A. L. d'Abreu, for giving us information about their patients. Miss M. S. Gradwell recorded histories in the homes of patients. The research was assisted by a grant from the Birmingham University Students' Social Services Fund.

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THE PLASMA LIPIDS IN CORONARY ARTERY DISEASE

BY

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In the vast majority of patients coronary artery disease is a manifestation of atherosclerosis. Many diseases that favour the development of atherosclerosis are associated with disturbances in the plasma lipids (Hirsch and Weinhouse, 1943; Gould, 1951), and the high concentration of cholesterol in the arterial plaques has focused attention on the relationship of lipid metabolism to atherosclerosis. The lipid composition of atherosclerotic plaques and of plasma is similar enough to suggest that the lipids of the plaques may have their origin in the plasma (Weinhouse and Hirsch, 1940; Buck and Rossiter, 1951) and labelled cholesterol studies have shown that this plasma lipid is, in fact, incorporated into the atherosclerotic plaque (Biggs *et al.*, 1952). Less comprehensive studies of the plasma lipids in normal subjects compared with patients with coronary artery disease have been made in the United States (Morrison *et al.*, 1948; Gertler *et al.*, 1950; Steiner *et al.*, 1952). It was thought that a larger study, precisely controlled in respect of age and sex, would be of value especially if conducted in Britain where the dietary habits differ to some extent from those elsewhere.

METHOD

The subjects were 200 consecutive admissions with coronary artery disease and 200 miscellaneous in-patient controls. In the coronary artery disease group, there was electrocardiographic confirmation of myocardial infarction in 170, and of ischæmia before or after the Master two-step test in 30 who presented clinically with angina of effort; any subject who lacked cardiographic confirmation of coronary artery disease was excluded. Adequate controls were very difficult to obtain from a hospital population, but were carefully selected from convalescent in-patients, who had no history or clinical features of atherosclerosis, cardiac, hepatic, metabolic, or renal disease, nor of any other condition known to influence the plasma lipids. The coronary artery disease group was completed first, and the mean age of each decade of both sexes was determined; the control group was then completed so that the mean age, and number of cases in each decade, would correspond with the coronary artery disease group.

In a small pilot study an irregular diurnal variation in plasma cholesterol was observed thus it was decided that all samples should be withdrawn between 8 and 8.30 a.m. in the fasting state. No blood sample taken during anticoagulant therapy has been included in this series. Similarly, no blood sample taken within five weeks of the occurrence of myocardial infarction has been included. All subjects were receiving a light ward or weight-reducing diet.

Plasma free and total cholesterol (hence ester cholesterol by difference) were estimated by the Sperry-Schoenheimer digitonin method as modified by Sperry and Webb (1950). Plasma lipid phosphorous was estimated by the molybdenum-blue method of Allen (1940). The phospholipid content of plasma has been calculated by multiplying the lipid phosphorus value by 25. The precise details of the analytical procedures have been reported previously (Oliver and Boyd, 1953). The spectrophotometer was calibrated each day using analytical reagent grade standards. Serial lipid determinations on the same plasma sample agreed to within ± 2 per cent. Repeated plasma lipid determinations on a group of normal males over many weeks showed less than 7 per cent variation.

RESULTS

Fig. 1 is a histogram of the age distribution of the 149 men and 51 women who made up the 200 consecutive admissions with coronary artery disease. Its pattern with the maximal incidence in

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men in the 50–59 age group, and in women in the 60–69 age group, is familiar. The ratio of men to women decreased from 4 to 1 in the 30–59 groups, to 2 to 1 in the 60–69 group, and 1 to 1 in the over 70 group.

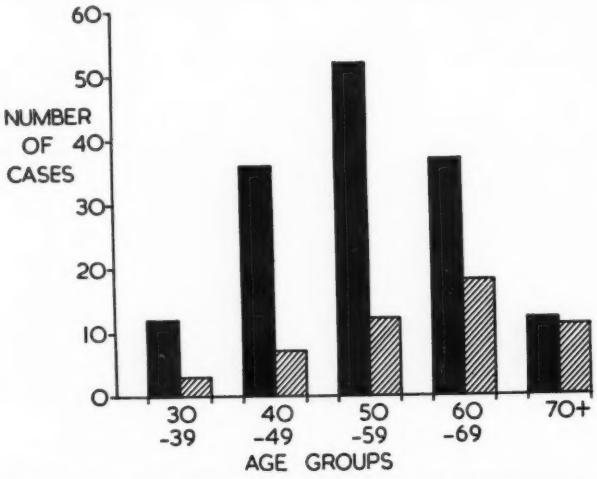

FIG. 1.—A histogram showing the age distribution of the 200 consecutive admissions with coronary artery disease. Black blocks represent men and shaded blocks represent women.

The results of the plasma lipids of each group were contrasted by decades and were expressed separately for the sexes; the standard errors of the means are shown in Fig. 2 to 5. Fig. 2 represents the mean plasma total cholesterol, and Fig. 4 the mean plasma total-cholesterol:phospholipid ratio, in the men. Table I shows the actual values of these means together with the standard deviations

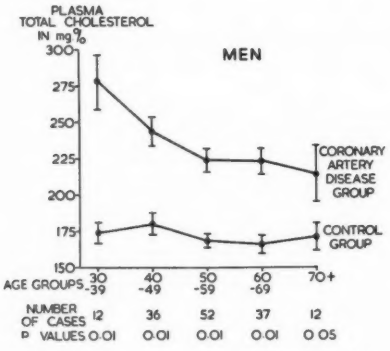

FIG. 2—The mean plasma total cholesterol values for men of the coronary artery disease group and of the control group. The number of cases in each group are indicated. Tests of significance at each decade are shown by the upper limits of the P values.

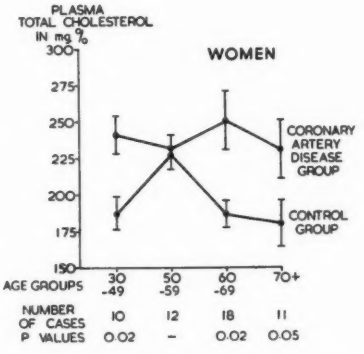

FIG. 3.—The mean plasma total cholesterol values for women of the coronary artery disease group and of the control group (see Fig. 2).

TABLE I

PLASMA TOTAL-CHOLESTEROL AND OTHER FINDINGS IN MEN

Decades	No.	Mean age	Plasma total-cholesterol in mg. per 100 ml.	Standard deviation	Range of plasma total-cholesterol	Plasma total-cholesterol: phospholipid ratio	Standard deviation	Range of cholesterol: phospholipid ratio
				Coronary Artery Disease				
30–39	12	36	278	±64	201–428	0·99	±0·12	0·79–1·23
40–49	36	45	243	±60	132–405	0·93	±0·14	0·58–1·16
50–59	52	54	224	±59	120–424	0·90	±0·12	0·63–1·17
60–69	37	64	223	±57	117–430	0·88	±0·14	0·53–1·17
70+	12	75	214	±66	134–340	0·91	±0·14	0·66–1·22
				Controls				
30–39	12	36	174	±22	127–206	0·80	±0·15	0·49–0·98
40–49	36	45	180	±33	110–234	0·84	±0·15	0·52–1·16
50–59	52	54	168	±30	106–230	0·82	±0·10	0·53–1·07
60–69	37	64	166	±42	100–265	0·80	±0·14	0·51–1·30
70+	12	75	171	±34	124–242	0·77	±0·12	0·54–0·90

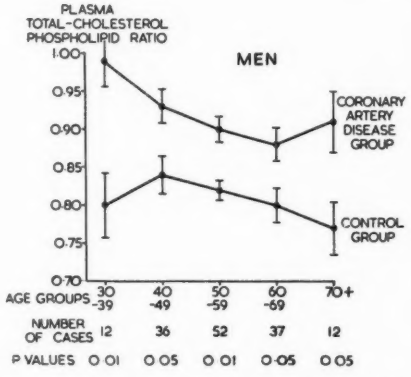

FIG. 4.—The mean plasma total-cholesterol: phospholipid values for men of the coronary artery disease group and of the control group. The number of cases in each group are indicated. Tests of significance at each decade are shown by the upper limits of the P values.

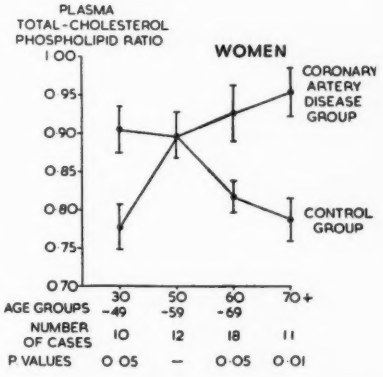

FIG. 5.—The mean plasma total-cholesterol: phospholipid ratio values for women of the coronary artery disease group and of the control group (see Fig. 4).

and ranges. There was significant elevation of plasma total cholesterol and plasma total-cholesterol: phospholipid ratio in all decades in the coronary artery disease group; this significance may, however, only be applied to the group of subjects and not to an individual as there were instances of overlap from one group into the other. Maximal elevation occurred in the earliest decade of the study in men with coronary artery disease. There was no progressive rise with increasing age in the value of plasma total cholesterol in the control group.

Fig. 3 represents the mean plasma total cholesterol, and Fig. 5 the mean plasma total-cholesterol: phospholipid ratio for the women; Table II shows the actual values of these means together with the standard deviations and ranges. As for the men, there was significant overall elevation of these values in all decades, except the sixth, and there was no progressive rise with increasing age in the

TABLE II

PLASMA TOTAL-CHOLESTEROL AND OTHER FINDINGS IN WOMEN

Decades	No.	Mean age	Plasma total-cholesterol in mg. per 100 ml.	Standard deviation	Range of plasma total-cholesterol	Plasma total-cholesterol: phospholipid ratio	Standard deviation	Range of cholesterol: phospholipid ratio
			Coronary Artery Disease					
30–49	10	42	241	±39	206–342	0·91	±0·11	0·75–1·09
50–59	12	54	232	±33	160–282	0·90	±0·09	0·80–1·14
60–69	18	64	251	±88	167–432	0·93	±0·16	0·59–1·22
70+	11	75	239	±65	188–360	0·96	±0·10	0·75–1·23
			Controls					
30–49	10	42	187	±36	135–248	0·78	±0·09	0·66–0·94
50–59	12	54	228	±40	164–295	0·90	±0·10	0·68–1·02
60–69	18	64	187	±40	143–270	0·82	±0·09	0·66–0·99
70+	11	75	180	±52	114–300	0·79	±0·09	0·69–0·92

control group. However, in women with coronary artery disease there was no hypercholesterolæmia in the earliest age group of this study. Moreover, in women in the sixth decade the mean plasma lipid results of both the control group and coronary artery disease group were identical.

It must be emphasized that the means of each decade are derived from separate groups, and thus it cannot be concluded that with advancing years the plasma lipids of an individual will necessarily follow any of these curves.

DISCUSSION

Provided the subjects of this study are representative of the coronary artery disease population and the normal population, these results show that plasma total cholesterol and the plasma total-cholesterol:phospholipid ratio are both raised in coronary artery disease in Britain; the observations of Gertler *et al.* (1950), Steiner *et al.* (1952), and other smaller studies conducted in the United States are thus confirmed. An exception to this generalization has occurred in this study in the sixth decade in women and will be discussed later.

While there is no doubt regarding the significance of the elevation of plasma total cholesterol in coronary artery disease, it has been suggested that the ratio of plasma total cholesterol to the plasma phospholipids may be a more important measurement of disturbance of lipid metabolism in atherosclerosis (Ahrens and Kunkel, 1949; Ladd *et al.*, 1949). These authors suggested that the plasma phospholipids may, along with other factors, stabilize the colloidal dispersion of plasma cholesterol. Hence a relative decrease in plasma phospholipids may favour cholesterol deposition. If the phospholipids have a protective action against cholesterol deposition, then, in order to maintain the stability of the colloids, any rise in plasma total cholesterol must be accompanied by a corresponding rise in the plasma phospholipids. In fact there was no corresponding increase in plasma phospholipids in the coronary artery disease group of this study, and thus there was elevation of the plasma total-cholesterol:phospholipid ratio. This confirms the observations made in coronary artery disease by Gertler *et al.* (1950), Morrison *et al.* (1950), Steiner *et al.* (1952) and others.

It is of interest that the most significant rise in plasma total cholesterol and the plasma total-cholesterol:phospholipid ratio in the coronary artery disease group occurred in men under 40. A greater degree of hypercholesterolæmia may be necessary for the premature development of coronary artery disease, and exposure to a high blood cholesterol for a short period may show the same deleterious effect on the coronary arteries that is produced by milder but more long-standing elevation. Duff and McMillan (1951), however, suggested that patients with hypercholesterolæmia and premature coronary artery disease should be grouped with those who suffer from

hypercholesterolæmia from other causes, and that they are not representative of most atherosclerotic subjects.

There was, in the control group of both sexes, no progressive rise in plasma total cholesterol with increasing age. The results obtained from the fourth decade onwards in this British study differ from the observations, also on normal subjects, in the much larger Minnesota series, which showed an upward trend of serum cholesterol with increasing age (Keys *et al.*, 1950); our results, however, correspond with the smaller series observed in Naples by the same author (Keys *et al.*, 1952). Both the Minnesota and Neapolitan studies and also a small British study of 46 subjects with a mean age of 22 years (Tanner, 1951) showed a rise in serum cholesterol with increasing age during the second and third decades, but it was not until the fourth decade, where our series started, that Keys' two groups diverged; subsequently our study corresponded to the Neapolitan group. Keys suggested that the difference between the Minnesota and Naples groups might be due to the lower fat and lower animal protein intake of the latter.

In women, in all decades except the sixth, the plasma lipid values of the coronary artery disease group differed significantly from the control group. In the sixth decade, however, the mean plasma total cholesterol and the mean plasma total-cholesterol:phospholipid ratio of the two groups were identical. The rise of these values in the control group above the values for adjacent age groups is significant ($P < 0.05$). There is at present no other comparable study of these lipid values with advancing years in normal women, but, on the assumption that this rise at the sixth decade is real, then their behaviour in a group of supposedly normal subjects is unexpected and requires consideration. Hypertension and obesity are more common after the menopause, but neither would seem to influence these observations; all the control subjects had a diastolic pressure of less than 90, and a morphological study employing a ponderal index assessment (Sheldon *et al.*, 1940), did not show any tendency to endomorphy in this decade in the controls. The rise in these plasma lipid values occurred in the decade immediately after the menopause, and might be related to the hormonal disturbance of the menopause and, in particular, to œstrogen withdrawal at that time. It has previously been suggested that these plasma lipid values may be influenced by endogenous œstrogen secretion in normal young women (Oliver and Boyd, 1953). Explanation of the significant fall in these plasma lipid values during the subsequent decades of the control group is not readily forthcoming. A variety of conditions commonly occur after the menopause, which, on the basis of our rigid criteria for the selection of controls, exclude subjects from the later decades of the control group; thus the subjects included in later decades are derived from a diminishing "population," which introduces a sampling error. It seems possible that any hormonal imbalance affecting the plasma lipids at or after the menopause may be temporary, and that subsequently, even although sex hormone secretion is minimal, the lipids may in some way regain their former equilibrium. If there is, in fact, a hormonal basis for the rise in these plasma lipid values in the control group, the coronary artery disease group is not similarly influenced, at any rate, in this decade. It is well known that coronary artery disease is uncommon before the menopause, and it is possible that subjects with established atherosclerosis and elevated cholesterol levels are not affected by the hormonal disturbance of the menopause in the same manner as normal women.

Conclusions

Plasma free and total cholesterol and plasma phospholipids were estimated in 200 subjects with electrocardiographic proof of coronary artery disease and in 200 controls, who were matched to the pathological group precisely in respect of age and sex.

There was significant elevation of the plasma total cholesterol and of the plasma total-cholesterol: phospholipid ratio in the coronary artery disease group at all ages and in both sexes, with the exception of the sixth decade in women.

Hypercholesterolæmia occurred in the small group of men with coronary artery disease under the age of 40.

There was no progressive rise in plasma total cholesterol or the plasma total-cholesterol:phospholipid ratio with increasing age in the control group of both sexes. At the sixth decade in

women the mean plasma total cholesterol and the mean plasma total-cholesterol:phospholipid ratio of the control group rose to the coronary artery disease group level.

Some of the relationships of these plasma lipid patterns to coronary artery disease are discussed.

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THE CLINICAL AND RADIOLOGICAL ASSESSMENT OF THE PULMONARY ARTERIAL PRESSURE IN MITRAL STENOSIS

BY

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The frequent association of pulmonary hypertension with symptomatic mitral stenosis has stimulated much investigation concerning its significance and the mechanism of its production. Two types are now recognized: passive hypertension, where the increased pressure in the left atrium and pulmonary veins and capillaries produced by the stenosed mitral valve is transmitted to the pulmonary artery; and active hypertensions, where much higher levels of pulmonary arterial pressure are due to an increased vascular resistance in the lungs (Bayliss *et al.*, 1950*a*; Eliasch, 1952; Lewis *et al.*, 1952). The causes of this increase in vascular resistance are not fully understood, but Parker and Weiss (1936), Larabee *et al.* (1949), Henry (1952), and Harrison (1953) have found thickening of the walls of the small pulmonary arteries, while Dexter *et al.* (1950), Holling (1952), and Ball *et al.* (1952) have suggested that reversible vasoconstriction may also occur. Angio-cardiography has demonstrated narrowing and irregularity of the smaller pulmonary arteries in patients with symptomatic mitral stenosis (Goodwin *et al.*, 1952; Actis-Dato *et al.*, 1952). The present investigation was undertaken to determine the significance of these changes, whether they could be detected on plain radiographs, and whether they were proportional to the pulmonary arterial pressure. The value of the symptoms, physical findings, and electrocardiographic signs, in estimating pulmonary arterial pressure was assessed by comparing them with the pressures measured by cardiac catheterization. An attempt was made to determine which of these methods provided the best estimate of the pressure.

METHODS

Fifty-one patients suffering from mitral stenosis of varying severity were studied. The series included patients with normal pulmonary arterial pressures and with all degrees of pulmonary hypertension. Thirty-five patients had aortic valve disease, but in all these mitral valve disease was the dominant lesion. Mitral incompetence, in association with stenosis, was diagnosed in 10 subjects, and in 4 of these was thought to be of greater hæmodynamic importance than stenosis. One patient had systemic hypertension in addition to mitral stenosis. Dyspnœa was graded according to the classification of the New York Heart Association (1939).

The clinical classification of pulmonary hypertension was as follows. *Grade O:* normal left ventricular impulse, normal second sound in the pulmonary area. *Grade I:* tapping impulse, gentle sternal lift, narrow splitting of the second heart sound with slight accentuation of the pulmonary element. *Grade II:* tapping impulse, marked sternal heave, narrow splitting of the second heart sound with more accentuation of the pulmonary element. A systolic murmur over the pulmonary area and a triple rhythm were not found frequently enough to be of diagnostic value.

Cardiographic evidence of right ventricular hypertrophy was graded as follows. *Grade O:* normal ventricular complexes with or without abnormal P waves or auricular fibrillation. *Grade I:* clockwise rotation (R smaller than S in V5), predominant R wave in aVR and in V4R, incomplete right bundle branch block. *Grade II:* R wave greater than S wave in V1, with ventricular activation time greater than 0·03 per second in V1; R wave smaller than S wave in V5, predominant R wave in aVR.

Cardiac Catheterization. Systolic and diastolic pressures in the pulmonary artery (or right ventricle) in the resting state were measured by strain-gauge manometer in 43 patients by the technique of Bayliss *et al.* (1950*b*), the maximum normal pressure being 30/15 mm. Hg.

Angiocardiography. Venous angiocardiograms were performed in 22 patients by the technique previously described (Goodwin *et al.*, 1952). Selective pulmonary arteriograms were carried out in a further 9 patients as follows: after sedation, a number 9 cardiac catheter was introduced into the right (or left) main pulmonary artery and the pressure measured. After an injection of atropin (1/100 of a grain), anæsthesia was induced by intravenous pentothal and maintained with gas, oxygen, and trilene. Twenty ml. of 70 per cent solution of diodone was injected through the catheter by means of a manually operated pressure pump. The radiographic technique was identical with that used for venous angiocardiography.

No adverse reaction occurred in any patient as a result of the injection of contrast medium into the pulmonary artery. Care was taken to ensure that the tip of the catheter did not pass beyond the right or left main pulmonary artery. General anæsthesia diminished the possibility of pulmonary artery spasm, sudden coughing, or movement. Venous angiocardiography was uneventful in all except one patient. This was a woman of 49 years with severe mitral stenosis and pulmonary hypertension, whose condition gave rise to no anxiety during or immediately after the angiocardiogram, but shortly after return to the ward she became cyanosed and pulseless, and died suddenly: there had been no reaction to a test dose of diodone. Autopsy confirmed the clinical diagnosis and there were widespread and severe occlusive changes in the smaller pulmonary arteries and arterioles. Pulmonary œdema was absent, and the exact cause of sudden death could not be ascertained.

Results

Angiocardiographic Appearances. As has been previously described (Goodwin *et al.*, 1952) the pulmonary arteries presented a distinctive appearance in patients with pulmonary hypertension. Enlargement of the main arteries was associated with narrowing, tortuosity, and irregularity of the peripheral branches, mainly at the bases, but more widespread when pulmonary hypertension was severe. In patients with normal pulmonary arterial pressures or a minimal increase, the main pulmonary arteries were normal or slightly enlarged and the peripheral branches appeared normal or showed minimal changes. The pulmonary veins were usually normal but sometimes enlarged. Selective pulmonary arteriograms demonstrated the arterial changes more clearly than did the venous angiocardiograms. The appearances of the left atrium have been noted elsewhere (Steiner and Goodwin, 1953) and will not be further mentioned here.

The Appearances of the Lungs on plain Radiographs. The main pulmonary arteries were found to be enlarged in patients with pulmonary hypertension, and as in the angiocardiograms, the peripheral branches were seen to be narrowed, predominantly at the bases (Fig. 1). The pulmonary veins were visible in some films, but were not sufficiently clearly outlined to permit any conclusions to be drawn. A fine mottling of the lung fields (Fig. 2), which from a study of the angiocardiograms did not appear to be arterial or venous in nature, was usually associated with significantly increased pulmonary arterial pressure. This mottling was enough in 16 patients to warrant the diagnosis of hæmosiderosis, the systolic pulmonary arterial pressure being above 100 mm. Hg in 5 of them, between 50 and 100 in 6, between 30 and 50 in 3, normal in one, and not measured in one. In 10 patients fine horizontal striations at the bases of the lungs in the region of the costophrenic angle were seen, similar to those ascribed to engorged lymphatic channels by Kerley (1951).

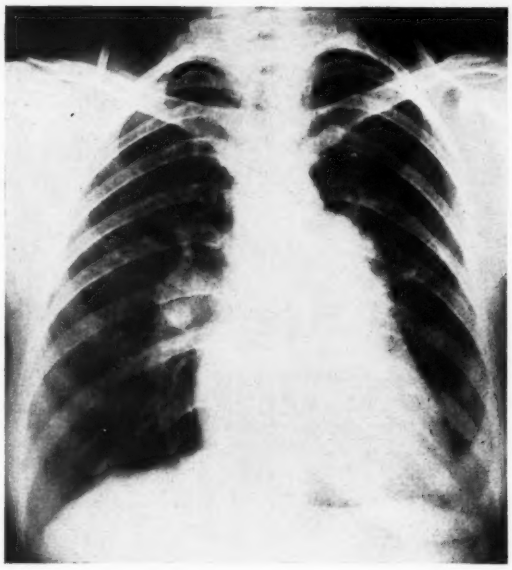


FIG. 1.—Six-foot postero-anterior radiograph of patient with severe pulmonary hypertension (P.A. pressure 130/70 mm. Hg). Great enlargement of main pulmonary artery and major branches, with narrowing and irregularity of peripheral branches.

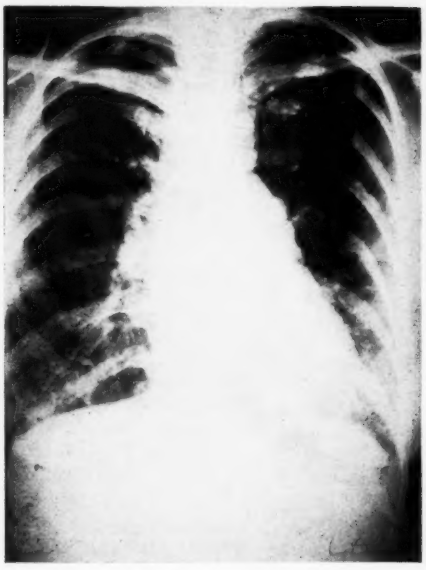


FIG. 2.—Six-foot postero-anterior radiograph of patient with pulmonary arterial pressure of 100/50 mm. Hg. Enlargement of main pulmonary artery and major branches, with narrowing of peripheral branches. Fine mottling in lower and mid zones of lungs.

The Comparison between the Angiocardiographic and the plain Radiographic Appearances of the Pulmonary Arteries. The appearances in angiocardiogram and plain film of the main pulmonary arteries and the first, second, and third divisions were compared in each of 22 patients, having regard to whether the branches were narrowed, normal, or enlarged. Fig. 3 shows that there was a positive correlation, most of the changes demonstrated angiocardiographically being detected on the straight film. Comparison was more difficult in those with moderately raised pressures than those with normal pressure or with severe pulmonary hypertension. Correlation between the angiocardiographic appearances and the straight radiographs was equally good in the 9 patients examined by angiocardiography or pulmonary arteriography, in whom the pulmonary arterial pressure was not measured.

The correlation was sufficiently good to permit the severity of the arterial changes to be graded by examination of the plain radiograph. Three grades of pulmonary arterial change were recognized:

Grade O, normal (Fig. 4 A and B); *Grade I*, enlargement of the main pulmonary artery, including the first divisions, with narrowing and tortuosity of the distal branches, the changes being confined to the bases of the lungs (Fig. 5 and 6); and *Grade II*, marked enlargement of the main pulmonary artery and main branches with more widespread peripheral changes (Fig. 7 and 8). The plain radiographs were assessed with consistent results by each of the authors separately.

The grade of arterial change in relation to the pulmonary arterial pressure in each subject in whom angiocardiography was carried out, can be seen in Fig. 3. Fig. 9 shows the arterial changes seen on plain radiographs, in a control series of 21 subjects upon whom angiocardiography was not performed, arranged in order of ascending systolic pulmonary arterial pressures. In both groups of patients the highest pulmonary arterial pressures tended to be associated with Grade II arterial

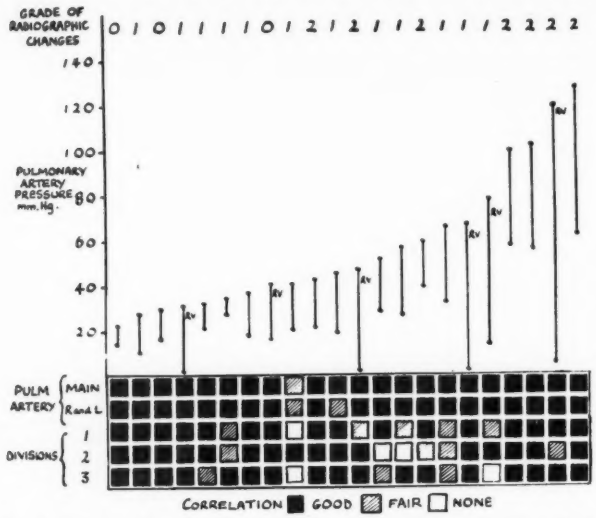
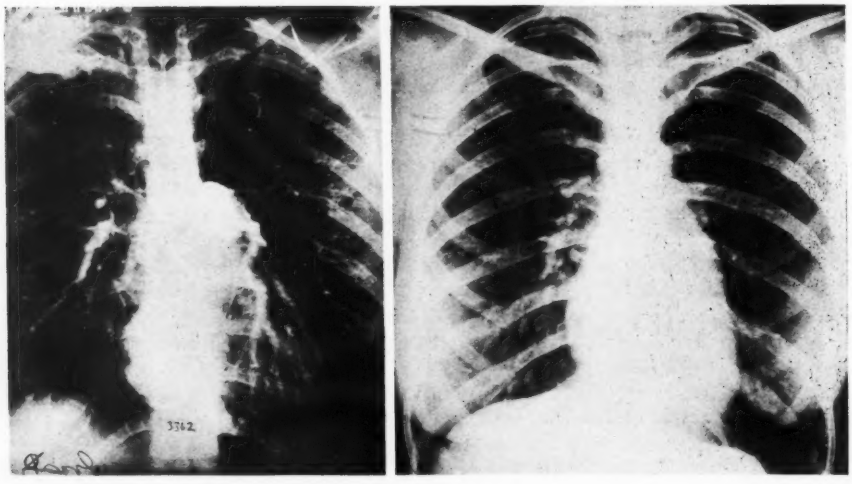
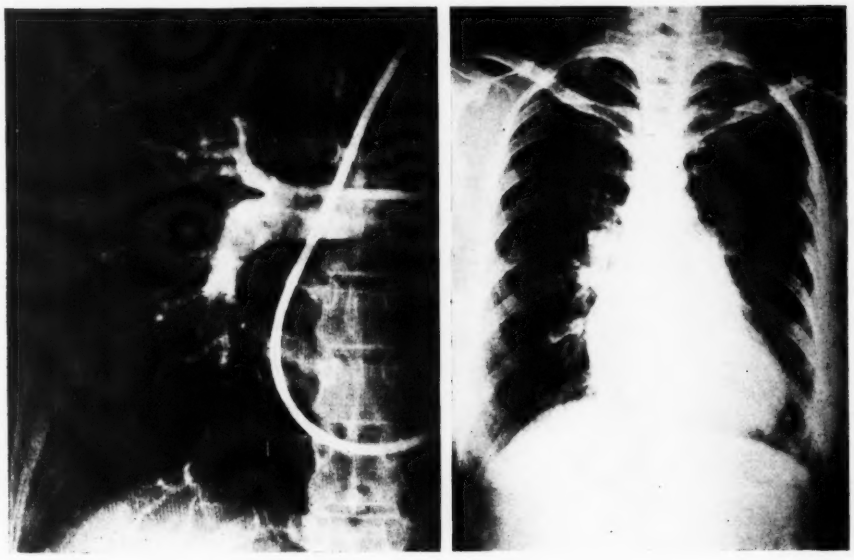


FIG. 3.—*Comparison between the pulmonary arterial pressure and the angiocardiographic and the plain film appearances of the pulmonary arteries in* 22 *patients with mitral stenosis.* In each, the appearances of the pulmonary arterial tree on the plain radiograph have been compared with the angiocardiogram, using the latter as a standard. The comparison between each branch in each patient is shown in the block diagram. The grade of arterial change as seen on the plain film in each case is shown at the top of the chart.



A B

FIG. 4.—(A) Venous angiocardiogram of patient with mitral stenosis but without pulmonary hypertension. The pulmonary arterial tree is normal, except for slight enlargement of the main trunk. (B) Six-foot postero-anterior radiograph of the same patient. The slight enlargement of the main pulmonary artery and the normal peripheral branches can be clearly seen.



A B

FIG. 5—(A) Selective pulmonary arteriogram of right lung of patient with pulmonary arterial pressure of 45/20 mm. Hg. Slight enlargement of right main pulmonary artery and some narrowing and tortuosity of the peripheral basal branches. (B) Same patient as (A). Six-foot plain radiograph of chest. Enlargement of the major branches of the pulmonary artery and narrowing of the basal peripheral branches can be seen.

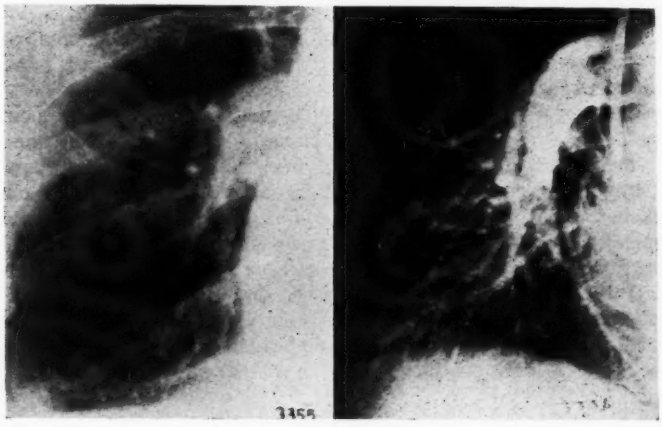


FIG. 6.—Comparison between the appearances of the pulmonary arteries of the right lower lobe in the plain radiograph and in the selective pulmonary arteriogram, in a patient with a pulmonary arterial pressure of 35/30 mm. Hg. Slight narrowing of the distal branches can be seen in both.

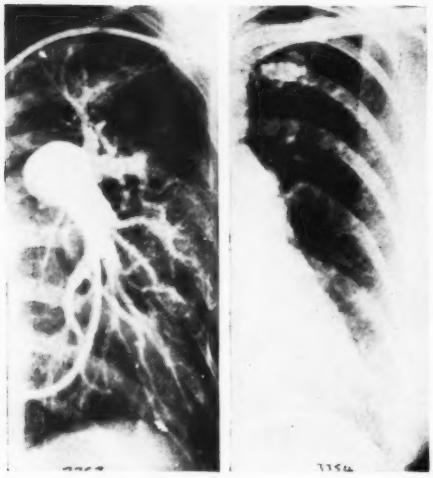


FIG. 7.—Same patient as Fig. 2. Comparison between the appearances of the left pulmonary arteries in the plain radiograph and in the selective pulmonary arteriogram. Enlargement of the left main pulmonary artery and marked narrowing of the distal branches, involving lower and mid zones, can be seen.

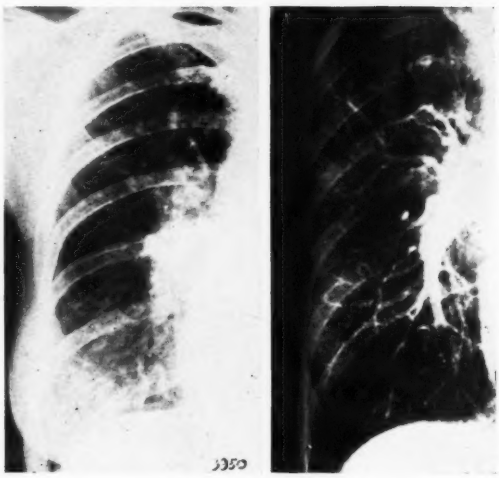


FIG. 8.—Comparison between the appearances of the pulmonary arteries in the right lung on the plain radiograph and in the selective pulmonary arteriogram, in a patient with a pulmonary arterial pressure of 60/40 mm. Hg. Enlargement of the main pulmonary artery is associated with generalized narrowing of peripheral branches. A fine mottling, which is not arterial in nature, can be seen at the right base in the plain film.

changes, while these abnormalities were usually absent in subjects with normal or only slightly raised pressures. Arterial changes were always present when the systolic pressure in the pulmonary artery was greater than 40 mm. Hg. There were 8 patients with a systolic pressure greater than 80 mm. Hg, all of whom had widespread narrowing of the peripheral pulmonary artery branches (Grade II). There were 6 patients with a normal arterial pattern and normal pressures: one of them had severe symptoms, and at operation tight mitral stenosis was confirmed and valvotomy has been followed by marked improvement.

The systolic pulmonary arterial pressure to the nearest 5 mm. Hg has been compared with the grade of symptoms, with the clinical grade of pulmonary hypertension, with the grade of arterial changes and with the cardiographic grade of right ventricular hypertrophy respectively (Fig. 10). The correlation between systolic pressure in the pulmonary artery and arterial changes was good. The correlation between the physical signs of pulmonary hypertension and pulmonary arterial pressure was rather better than that between symptoms and pressure, but it will be noted that systolic pressures of over 70 mm. Hg were never associated with symptoms of less than Grade III severity, whereas Grade III symptoms were frequently found in association with pressures below 70 and sometimes below 50 mm. Hg. Correlation between systolic pressure in the pulmonary artery and electrocardiographic signs of right ventricular hypertrophy was poor. Correlation between pulmonary arterial mean pressure and grade of arterial changes was the same as when the systolic pressure was used.

DISCUSSION AND CONCLUSIONS

The results indicate that narrowing of the peripheral pulmonary arteries, in association with enlargement of the main and proximal branches, occurs in patients with mitral stenosis and pul-

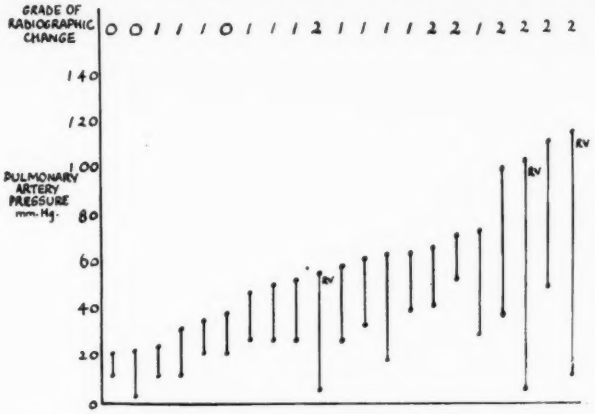


FIG. 9.—Comparison between the pulmonary arterial pressure and the plain film appearances of the pulmonary arteries in 21 patients with mitral stenosis, upon whom angiocardiography was not performed. The extent of the arterial changes seen on the plain radiograph is shown at the top of the chart.

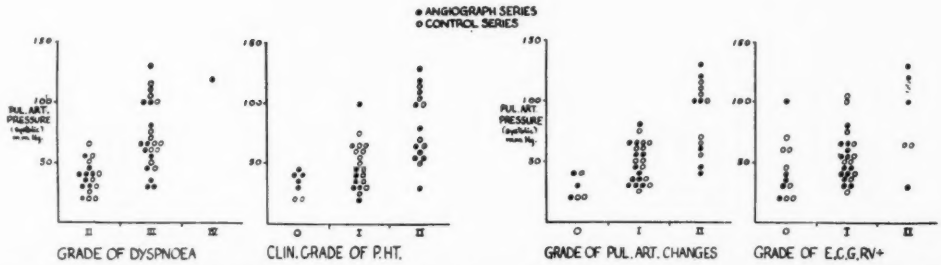


FIG. 10.—The systolic pulmonary arterial pressure (to the nearest 5 mm.) in 43 patients, plotted against the grade of dyspnœa on effort (New York Heart Association classification), the clinical grade of pulmonary hypertension, the grade of pulmonary arterial changes seen on the plain radiograph, and the electrocardiographic grade of right ventricular hypertrophy, respectively.

Closed circle represents patient with angiocardiogram. Open circle represents patient without angiocardiogram. P.H.T.=pulmonary hypertension. R.V.+=right ventricular hypertrophy.

monary hypertension. These changes can be detected by careful inspection of a plain radiograph of the chest, and their extent is a guide to the level of the pulmonary arterial pressure. Although some overlap inevitably occurs, patients can be placed in three groups: (1) a " minimal " group in which the systolic pulmonary arterial pressure is below 40 mm. Hg, and the arterial changes are absent or slight; (2) an intermediate group, in which the pressures range approximately from 40–70 mm. Hg, and arterial changes are always present, usually confined to the bases; and (3) a severe group in which pulmonary arterial systolic pressures of more than 70 mm. Hg and the arterial changes were widespread.

In no case have changes been seen in the mid-zones or apices of the lungs in the absence of concomitant basal changes, indicating that the arterial narrowing begins at the bases and then involves progressively more and more of the pulmonary arterial tree. Harrison (1953) has shown a similar distribution of organic narrowing on post-mortem angiocardiograms in subjects with mitral stenosis and severe pulmonary hypertension. He has also noted the absence of such changes in some cases

known to have had high pulmonary arterial pressures. In these, active constriction during life must have been the cause of the narrowing.

It is interesting to note that the level in the pulmonary arterial tree where we observed narrowing is that at which the arteries have a predominantly muscular wall, while the dilated proximal arteries have elastic walls with relatively little muscle.

In our view the presence of arterial changes must be considered as one of the indications for valvotomy, since it is very probable that the process is progressive and will lead to a further rise in the pulmonary arterial pressure and deterioration in effort tolerance. Absence of radiological arterial changes and of pulmonary hypertension is unusual in the presence of severe symptoms and occurred in only one patient, in whom operation confirmed tight mitral stenosis.

It is suggested that the term " pulmonary congestion " be confined to the appearances seen in congestive heart failure and pulmonary œdema. In severe mitral stenosis without failure the main pulmonary arteries are enlarged, but the peripheral branches are actively narrowed rather than passively congested: the term congested pulmonary arteries is therefore incorrect.

Recognition of the arterial changes on the plain radiograph permits greater accuracy in the estimation of the pulmonary arterial pressure than has hitherto been possible at the bedside by clinical means. Cardiac catheterization may therefore be omitted in many patients, unless special problems are present.

Summary

Fifty-one patients with mitral stenosis and varying degrees of pulmonary hypertension have been studied. In 31 of these, the pulmonary vascular pattern was investigated by venous angiocardiography or pulmonary arteriography.

In patients with pulmonary hypertension, the main arteries were found to be enlarged and the distal branches narrowed, irregular, and tortuous, especially in the lower lobes. The severity and extent of these changes bore a close relation to the degree of pulmonary hypertension.

The changes shown by angiocardiography could be detected on the plain film and were a better guide to the pulmonary arterial pressure than were the symptoms or clinical signs. The cardiographic signs of right ventricular hypertrophy gave little indication of the degree of pulmonary hypertension.

We wish to acknowledge the help of Professor J. McMichael and Dr. C. V. Harrison in the preparation of the paper, and to thank Mrs. Angela Birbeck for the tables, and Mrs. Connolly and Mr. Kemp for the radiological reproductions.

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LÆVOCARDIA WITH TRANSPOSITION OF THE ABDOMINAL VISCERA

BY

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The revival of interest in congenital heart disease is reflected by the increasing number of reported cases with transposed abdominal viscera and a normally situated heart.

Incidence. The condition is rare in ordinary practice. After viewing over 250,000 miniature chest radiographs, Nash (1952) cannot remember having seen such a case, and the experience of Morgan (1952), based on 150,000 miniature films and 50,000 full-size radiographs, is similar. They are careful to point out the limitations of this method in discovering the abnormal situation of the abdominal viscera, and this is in accordance with our own experience, that the shadow of gas in the stomach may sometimes be invisible on standard films so that transposition may be apparent in only one of a series of pictures. The rarity of this condition is, however, confirmed by Hills (1952) who cannot remember seeing a single case in the course of more than 20,000 routine barium meals.

We have studied 14 patients under our care and 19 others reported since the subject was reviewed by one of us (Forgacs, 1947) in an attempt to discover whether these defects conform to any common pattern. Our 14 patients were seen among 1130 patients with congenital heart disease, 12 among 670 cyanotic, and 2 among 460 acyanotic patients. In 4 of these the results of necropsies were available; angiocardiography had been carried out in 6 others and cardiac catheterization in 5 of them, but in 4 no special investigations have yet been performed so that the diagnosis must remain very uncertain. The 19 reported are single cases by Del Carril *et al.* (1949), Robinson and Garfinkle (1950), Tanner-Cain and Crump (1951), Case 2 of Hardy (1948), two cases by Thomson (1950), five cases by Doliopoulos and Maillet (1952), and eight cases by Young and Griswold (1951). Case 1 of Hardy is excluded because subsequently he was investigated by us and the findings and necropsy are reported as our Case 9. The two cases of Donzelot *et al.* (1950) were included as Cases 1 and 2 of Doliopoulos and Maillet (1952).*

Of this total of 33 cases, 10 came to necropsy (Tables I and II): among the others cardiac catheterization and angiocardiography were carried out in 9 and angiocardiography alone in 6 (Tables I and III); and in 7 of these and in 1 other the findings at operation were also available. The data are sufficient for analysis of at least some of the features of this uncommon type of heterotaxy.

Associated Defects. When the abdominal viscera are transposed and the heart is on the left, it is nearly always abnormal. There are two or three reported cases where the heart is said to have been normal but Geipel's Case 2 is the only one with necropsy and the only reference to this that we have found (Schelenz, 1909) gives no details. Among the recent cases with necropsies that of Tanner-Cain and Crump (1951) is the only one that makes no mention of any congenial defect. This was a child who was cyanosed at birth and died when three days old: at necropsy " the heart

* Doliopoulos has kindly informed us that in his paper the case references to Donzelot *et al.* (1951) should be to Doliopoulos and Maillet (1952), and that in Case 3 the superior vena cava was on the right and entered the right atrium and the ductus arteriosus was not patent.

was normally placed and extremely dilated with immense thickening of the myocardium and endocardium " but the relationship of the great veins to the atria or of the ventricles to the main arteries is not described.

Generally in these cases there are complicated defects and an accurate diagnosis is notoriously difficult. Our attempt to discover a common pattern has succeeded only partially but they can be divided into two groups. In the first the superior vena cava and the venous atrium follow the abdominal viscera and are transposed, which obviously leads to great difficulty in the development of a heart that can function reasonably well. In the second the superior vena cava and the venous atrium are not transposed and should, therefore, have a normal relationship to the rest of the heart so that the circulation should be normal—a finding that is, in fact, very rare. In the former the P wave in lead I is inverted, while in the latter it is upright (Campbell and Reynolds, 1952). In the former a veno-arterial shunt is left-to-right, and in the latter it is right-to-left as normally. In both groups there are likely to be atrial and ventricular septal defects, sometimes with a single atrium or ventricle, complete or partial transposition of the aorta and pulmonary trunk, and pulmonary stenosis or atresia: there may also be complicated abnormalities of the great veins. We think it important to discuss these groups separately.

Cases with an Inverted PI and the Venous Atrium on the Left

Our cases from this group with other reported cases where similar investigations had been carried out are summarized in Table I.

Case 1 (D.P. O405). This boy, aged 3, was cyanosed from infancy and had never crawled. As he was anæmic (hæmoglobin 62%), the obvious cyanosis and clubbing must have indicated a very low oxygen saturation; and he had always been liable to attacks, in which he was almost unconscious, often four or five times a day. He died suddenly at the age of 3 during one of these attacks.

No murmurs were heard and the pulmonary second sound was faint. The heart was large (cardio-thoracic ratio (c.t.r.) 62: m.t.d. 10/16 cm.) with a very broad pedicle (Fig. 1A); it was on the left side but the liver and stomach were transposed. Radioscopy showed oligæmic lung fields and displacement of the aorta forward and to the right. The electrocardiogram (Fig. 2) showed some right ventricular preponderance: PI was small and inverted and PII and PIII were large and upright.

Necropsy. Both the superior and inferior venæ cavæ were on the left and entered the left atrium. There was only a small slit patency of the atrial septum. The left atrium communicated through a

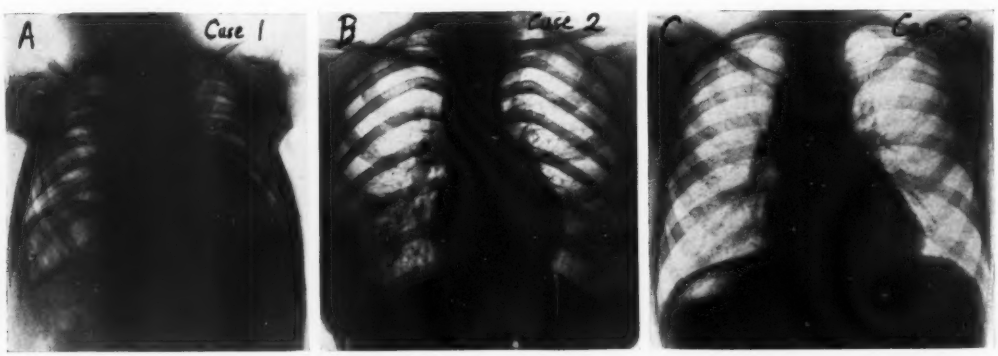

FIG. 1.—Teleradiograms from three cases with the venous atrium on the left. (A) Case 1, with a large heart and a broad pedicle. (B) Case 2, with a rather small heart. (C) Case 3, with a normal-sized heart. The aortic arch is right-sided in all these three, and this is nearly always so when the venous atrium is on the left. A barium swallow showed that the stomach was on the right in all these patients and the air bubble can be seen in (A) and (C).

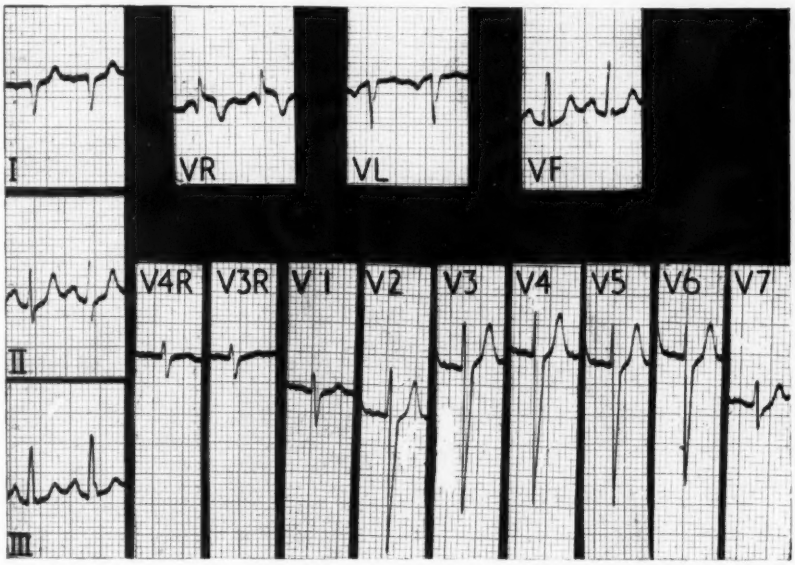

FIG. 2.—Case 1. Electrocardiogram showing inverted PI and less evidence of right ventricular preponderance than is usual. Standardization 1 mV.=0·5 cm. in chest leads, V4R to V7.

tricuspid valve with the larger ventricle that was placed posteriorly and on the left side. The outflow tract ran to the right to a high ventricular septal defect and the pulmonary trunk over-rode this.

The right atrium was small and posteriorly placed; it received the pulmonary veins and communicated through a *bicuspid* valve with the smaller ventricle on the right. The aorta arose from the extreme right of this ventricle and formed a right-sided arch. The pulmonary trunk arose behind and to the left of the aorta and over-rode the septal defect; the pulmonary valve was bicuspid and stenosed.

The lungs were transposed like the other viscera, the left having three lobes and weighing more than the right. There was situs inversus of all the abdominal viscera.

Case 2 (K.L. O428). This girl, aged 19, was cyanosed from the age of six weeks, and did not walk until she was 4 years old. She had always been breathless and, though she could walk a mile, had to stop every 50 yards for a rest. She did not squat. She had some degree of arachnodactyly.

Cyanosis and clubbing of the fingers were severe. A soft systolic murmur was loudest in the fourth left intercostal space close to the sternum, and the pulmonary second sound was normal. The heart was not enlarged (c.t.r. 46: m.t.d. 11·0/24 cm., Fig. 1B). Radioscopy confirmed the reversed position of the stomach and liver, oligæmic lungs, and a right-sided aortic arch. The cardiogram (Fig. 3) showed an inverted PI and S waves only from V1 to V5 so there may have been some slight hypertrophy of both ventricles. The red cell count was 8·7 million and hæmoglobin 137 per cent.

Catheterization showed that the superior and inferior venæ cavæ drained into the left atrium (O_2 saturations 61–67%). This communicated through a sizeable septal defect with the right atrium which received the pulmonary veins. From it the catheter entered the right (mixed arterial) ventricle where the systolic pressure was 120 mm. Hg and the arterial O_2 saturation 84 per cent compared with 75 per cent in the systemic arteries: it could not be passed into any exit from this or into the left (venous) ventricle.

Angiocardiography confirmed filling of the left atrium from a left-sided superior vena cava (Fig. 13A). Four seconds after the injection the aorta was opaque and at five seconds the pulmonary arteries were outlined.

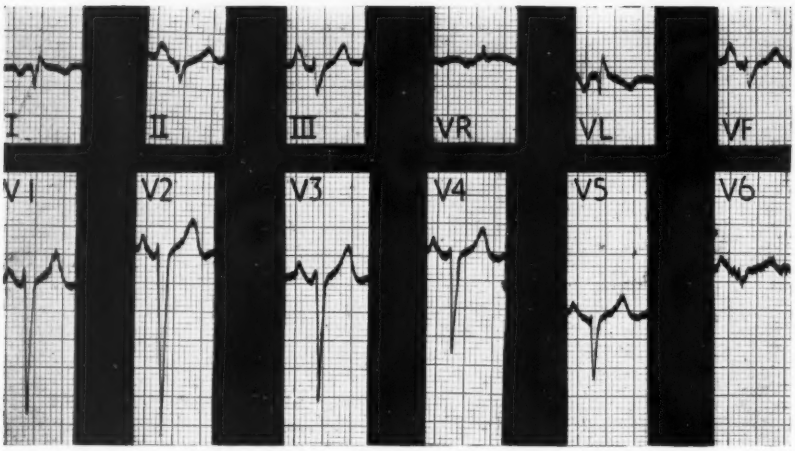

FIG. 3.—Case 2. Electrocardiogram showing inverted PI and no certain right ventricular preponderance, as there is low voltage in the standard and unipolar limb leads, large S waves only, from V1 to V5, and smaller S but quite insignificant R waves from V5R to V3R. Standardization 1 mV. = 1·0 cm. in all leads.

A complete diagnosis cannot be made. The atria are reversed and there is a large atrial septal defect. Pulmonary stenosis is supported by the oligæmic lungs. There is a free shunt from the venous side to the aorta but it is not clear whether it arises from the left (venous) ventricle or overrides this, or even from a right ventricle that is partly venous from a left-to-right shunt through the atrial septal defect. Two years later Mr. R. C. Brock was unable to find any pulmonary artery on the left side for a subclavian-pulmonary anastomosis. Attempts were therefore made to improve the collateral circulation over the pleura and six months later she seems to be somewhat improved.

Case 3 (L.H., P105). This boy, aged 14, was cyanosed from birth. When seen, he was attending an ordinary school but could only walk a mile on the level and was not playing any games.

He was small, deeply cyanosed, and had severe clubbing of the fingers. A harsh systolic murmur was widely conducted and was heard best in the third left intercostal space close to the sternum; the second sound was accentuated. The blood pressure was 110/80. The heart was normally situated and was not enlarged (c.t.r. 51: m.t.d. 12·5/24·6 cm. Fig 1C), the stomach was under the right costal margin, and the liver was palpable on the left side. The cardiogram (Fig. 4) showed right ventricular preponderance, PI was inverted (except in one record) and PII and PIII were upright. The hæmoglobin was 110 per cent and the red blood cells were 6·4 million.

Cardiac catheterization from the left arm proved that the superior and inferior venæ cavæ were on the left and drained into the left atrium. From here it entered a venous left ventricle but could not be advanced far (Fig. 5A). The left atrium also communicated through a large septal defect with the right atrium which received one and probably all the pulmonary veins (Fig. 5B). The catheter passed from the right atrium into the right ventricle both of which contained blood of a much higher oxygen saturation (78–80%) than the left side of the heart (66–68%). Neither the aorta nor the pulmonary trunk could be entered, but judging by the O_2 saturation of the aorta which was 78 per cent, it came mainly from the right ventricle, which had the same systolic pressure as the systemic arteries.

The angiocardiogram confirmed that the left atrium filled from a left superior vena cava but was at a rather high level for a venous atrium (Fig. 13B). There was a large communication between this and the right atrium, so that the heart seemed generally filled at 3 seconds. The aorta, situated well to the right and with a right-sided arch, became opaque at 4 seconds and the pulmonary arteries

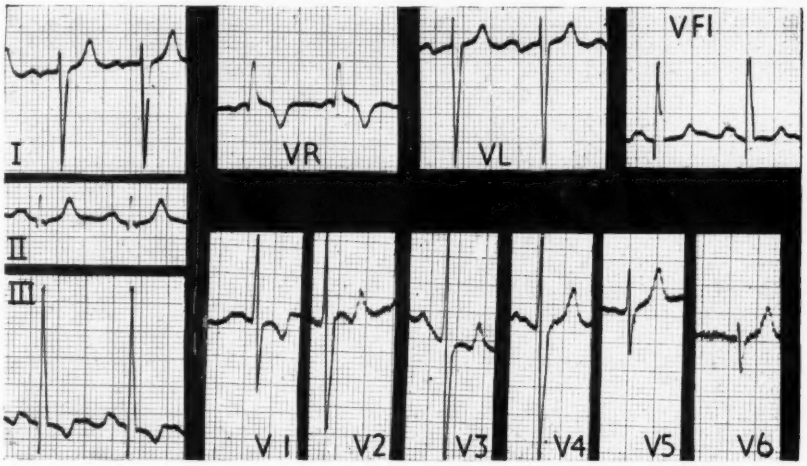

FIG. 4.—Case 3. Electrocardiogram showing inverted PI and the more usual evidence of right ventricular preponderance. Standardization 1 mV. = 1·0 cm. in all leads.

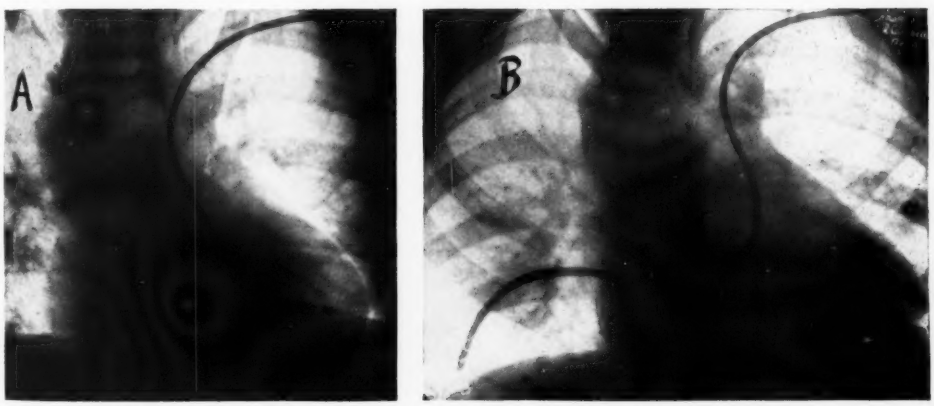

FIG. 5.—Catheter demonstration of the venous atrium on the left side. (A) The catheter has passed down the left S.V.C. to the left atrium, and to the left (venous) ventricle. (B) The catheter has passed through an atrial septal defect to the right atrium and thence into a pulmonary vein. Case 3.

were opaque between 2–4 seconds. The pulmonary trunk was not seen, but the pulmonary blood flow was thought to be little, if at all, diminished.

The diagnosis is incomplete. The arterial and venous sides of the heart are reversed; there is a large atrial septal defect; and the aorta is thought to arise from the right ventricle. He is now 17 and has kept well during the last three years.

Case 4 (R.W. O556). This girl, aged 7, was cyanosed from birth and until the age of 5 years could not walk more than 50 yards and used to squat. She then improved and, when seen at the age of 7, could walk a quarter of a mile. She was mentally backward and moderately cyanosed with severe clubbing of the fingers and toes. There was a prominent venous pulse in the neck.

TABLE I

CASES WITH THE VENOU

Case	Age and sex	Necropsy N Angioc. A Catheter C Operation O	Inf. V.C.	Sup. ven. cav.		Pulm. veins	A.S.D.	V.S.D.	Aortic arch
				R.	L.				
Our Case 1	3M	N	LA	Abs.	LA	RA	Slit P.F.O.	++	R
Young and Griswold, Case 1	2F	NO	LA	Abs.	LA	RA	P.F.O.	++	R
Our Case 2	19F	ACO	LA	—	LA	RA	+++	?	R
Our Case 3	14M	AC	LA	—	LA	?RA	++	?	R
Our Case 4	7F	ACO	LA	—	LA	RA	++	?	R
Our Case 5	4F	A	?LA	?	LA	?	++	?	R
Doliopoulos and Maillet (1952), Case 4	6F	A	?LA	?	LA	?	?	?	L

* Neither aorta nor pulmonary trunk were entered on cardiac catheterization.
† Generally inverted but sometimes upright with PII and PIII deeply inverted.

A harsh systolic murmur and a loud single second sound, which was probably aortic, were heard in the pulmonary area. The heart was normally situated and large (c.t.r. 65, m.t.d. 12·8/19·4 cm., Fig. 7A) with a broad pedicle: on screening both ventricles seemed large and the aorta arose well to the left and anteriorly; it was broad and unfolded and passed nearly horizontally to the right, forming a right-sided aortic arch. The lungs were oligæmic. The reversed situation of the liver and stomach was confirmed. The cardiogram showed right ventricular preponderance and the P waves were generally inverted in lead I but sometimes there was a change of pacemaker and then they were upright in lead I and inverted in leads II and III. The hæmoglobin was 136–160 per cent.

Catheterization from the left arm showed that the superior and inferior venæ cavæ entered a left venous atrium (Fig. 6A). From it the catheter passed directly into a venous ventricle on the left and thence into the aorta: the oxygen saturation at these three sites was much the same (77%, 77%, 80%). The right atrium (O_2 saturation 89%) and one of the pulmonary veins were entered through an atrial septal defect (Fig. 6E). The pressure in the left (venous) atrium (19/–4) was a little higher than in the right (arterial) atrium (14/–2 mm. Hg). Neither the second ventricle nor the pulmonary trunk could be entered.

Angiocardiography, from the right arm, confirmed that the left superior vena cava drained into the left atrium (Fig. 13C). Diodone passed at once to the right atrium through a large septal defect, and after 3 seconds the large ventricular cavity that extended to the apex and the arch of the aorta was opaque. The pulmonary arteries began filling at 4 seconds and were well seen at 5 seconds, though it was not clear how they arose.

At thoracotomy, Mr. Holmes Sellors thought there was a common arterial trunk, possibly with the right pulmonary artery arising from it: a right subclavian-pulmonary anastomosis was made.

ATRIUM ON THE LEFT SIDE

Origin of aorta	Origin of pulm. trunk	Pulm. orifice	Lungs	EC	PI	Remarks
From R of RV	Behind aorta from RV; over-riding LV	PVS	Oligæmic	Some RVP	Inv.	RA, RV arterial. LA, LV venous. Aorta from RV but PT stenosed and over-riding
From RV mainly but over-riding LV	Fibrous cord from LV	Atresia	Oligæmic	RVP	No EC	RA, RV arterial. LA, LV venous. Pulm. atresia and PDA
Receives venous blood *	?*	?PS	Oligæmic	S only V1 to V6	Inv.	RA arterial. LA venous. Large ASD. ?PS
From RV mainly. Receives venous blood *	?*	?	?Normal	RVP	Inv.	RA, RV arterial. LA, LV venous. Large ASD
Partly from LV (passage of catheter)	?	?PS	Oligæmic	RVP	Inv.†	RA, RV arterial. LA, LV venous. Aorta from LV
Receives venous blood	?	?	Oligæmic	LPV	Inv.	?RA, arterial. LA venous. ?Tricuspid atresia. ??Dextrocardia
From R. side. Receives venous blood	?	?	?Normal	RVP	Inv.	?

Six months after the operation her capacity and colour were better and after two years there was further improvement.

In this case the reversal of the arterial and venous atria was confirmed by catheterization and angiocardiography. There was a large atrial septal defect, and the lungs were oligæmic.

Case 5 (S.M., O266). This girl was cyanosed from birth and was first seen at the age of 7 months. During the first few months of life she had several attacks in which she became stiff and panted for breath, but these subsequently ceased. When 4 years old she was still unable to walk. She had intense cyanosis with severe clubbing of the fingers.

A systolic murmur was heard, loudest towards the apex, and a slight thrill was felt. The pulmonary second sound was normal. The heart was normally situated but rather central: it was not generally enlarged (c.t.r. 46, m.t.d. 7·6/16·5 cm., Fig. 7B) but on screening the left ventricle was enlarged, and the lungs looked oligæmic. The stomach was on the right but the liver seemed to be, at least partly, on the right also. The cardiogram showed an inverted PI and left ventricular preponderance.

Angiocardiography showed that the superior and inferior venæ cavæ and the venous atrium were all on the left (Fig. 13D). Diodone passed from the left atrium to the right and the aorta filled quickly. It was so much on the right that a right-sided arch was diagnosed and, although it curved to the left, it passed downwards on the right side, at least as far as the level of the diaphragm. The pulmonary trunk was not seen but the left pulmonary artery was filling at $1\frac{1}{2}$ seconds.

The clinical diagnosis is tricuspid atresia, though pulmonary stenosis with an unusual degree of rotation of the heart is not excluded. Although the heart is thought to be on the left it is possible that there is really dextrocardia with the heart rotated back to the left side.

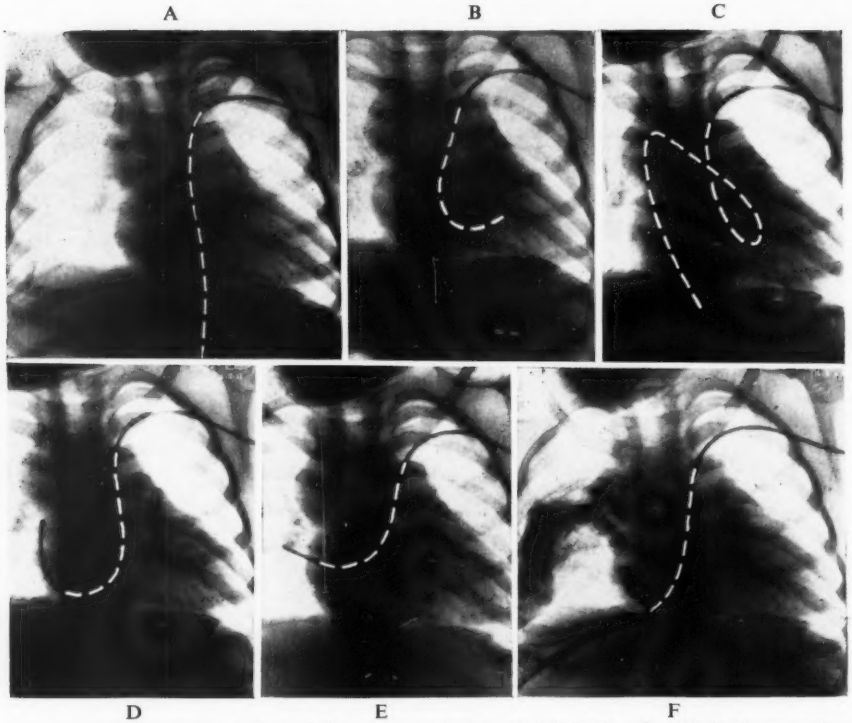

FIG. 6.—Catheter demonstration of the venous atrium on the left in Case 4. (A) Catheter passing down the left S.V.C. through the left atrium into the I.V.C. which also entered the left atrium. (B) Catheter passing from the left atrium to the left ventricle. (C) Catheter passing on from the left ventricle to the aorta and round the right-sided arch into the descending aorta which lies on the left below the diaphragm. (D) and (E) Catheter passing from the left to the right atrium through an atrial septal defect and outlining the border of this chamber (D) and entering a pulmonary vein (E). (F) Catheter passing from the left atrium, possibly via the right atrium, to the hepatic veins shown up by the injection of diodone. The hepatic veins may enter a different atrium from the inferior vena cava or the left atrium may extend more to the right in its lower part.

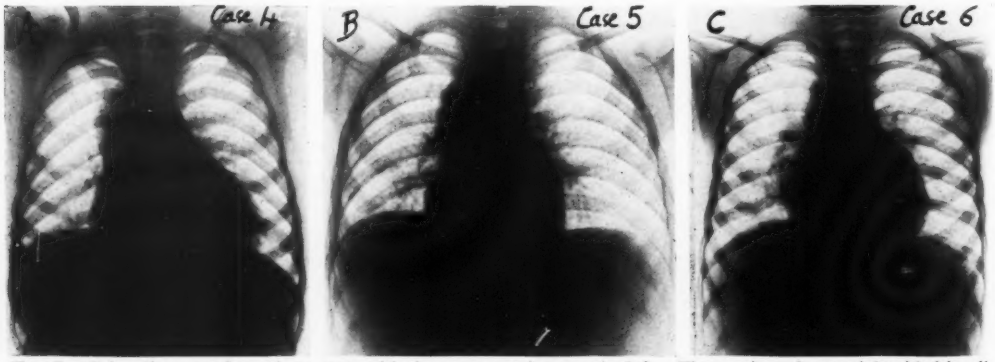

FIG. 7.—Teleradiograms from three cases with the venous atrium on the left. The aortic arch was right-sided in all three. (A) Case 4, with a rather large heart and broad pedicle. (B) Case 5, with a rather small heart and probably with tricuspid atresia. (C) Case 6, with some enlargement of the heart and left ventricular preponderance: she was one of the rare acyanotic patients and was thought to have congenital aortic stenosis.

Other Cases with P inverted in lead I

One other case of our own and Case 1 of Thompson (1950) belong to this group because of the inverted PI, but they are not included in the discussion or in Table I because no special investigations had been carried out.

Case 6 (B.T., O851). This girl, aged 4, looked healthy and had no disability, but congenital heart disease had been diagnosed when she was 3 weeks old. When 4 years old there was no cyanosis nor clubbing of the fingers. A thrill and systolic murmur were found, maximal in the right second intercostal space, and the second sound was normal. Her blood pressure was 100/70. The heart was normally situated and enlarged (c.t.r. 56: m.t.d. 9/16 cm.), mainly the left ventricle (Fig. 7C). The aortic arch was right-sided. The blood supply to the lungs was normal. The cardiogram showed left ventricular preponderance and the P wave was generally inverted in lead I, but once it was upright, probably with a change of pacemaker. The liver was palpable under the left costal margin, and on screening the stomach was seen under the right diaphragm. The provisional diagnosis was congenital aortic stenosis.

Cases with an Upright PI and with the Venous Atrium on the Right as Normally (Tables II and III)

Case 7 has been fully reported (Campbell *et al.*, 1952). A frail little boy, 5 years old at the time of his death, he had been cyanosed from birth and could not walk much more than 25 yards. The heart was large (c.t.r. 57) and there was a continuous murmur high up on the left side. The cardiogram showed an upright PI, inverted PII and PIII, and evidence of right ventricular hypertrophy. He died after a subclavian-pulmonary anastomosis.

Necropsy. The heart was bilocular. There were gross abnormalities of the veins, as the drainage from the lower half of the body was through the azygos vein to the right superior vena cava (Fig. 14A). A left superior vena cava was also present and passed through a greatly dilated coronary sinus to enter the right side of the common atrium. The aortic arch was left-sided.

Case 8 has been fully reported (Case 3 of Campbell *et al.*, 1953). She was 4 years old and had been severely cyanosed from birth. She could only walk 100 yards, but did not squat. There was a harsh systolic murmur and a faint thrill in the third left space. The heart was enlarged (c.t.r. 61) and sabot-shaped with a deep pulmonary bay. The aortic arch was left-sided. The cardiogram supported right ventricular preponderance and PI was upright. The hæmoglobin was 138 per cent. Angiocardiography showed that the superior vena cava and the venous atrium were on the right (Fig. 14B). She died after a subclavian-pulmonary anastomosis.

Necropsy. The heart lay normally on the left side. The systemic veins drained normally into a right atrium which opened by a tricuspid valve into a single ventricle. The pulmonary trunk arose to the left of the aorta, and there was pulmonary valvular stenosis. A single pulmonary vein from both lungs drained into the left atrium, from which the only exit was a slit-like opening in the atrial septum to the right atrium and thence to the common ventricle. The right lung had four lobes and the left had three. The stomach was on the right side and the gall bladder was on the left, but the liver lay on both sides.

Case 9 (A.M., O146). Cyanosis was first noticed when he was 6 months old. On a warm day he could sometimes walk 50 yards but in cold weather he could not get about at all: he squatted sometimes but not regularly. He was first seen when he was one year old and his condition was unchanged for the next three years, but became worse during his fifth year.

He was deeply cyanosed and had severe clubbing of the fingers. A widely conducted systolic murmur, followed by a single, loud and palpable second sound was heard in the pulmonary area. There was also systolic pulsation here, but after radioscopy this was rightly thought to be due to the aorta and not the pulmonary trunk. Screening showed a small, normally situated heart (c.t.r. 48: m.t.d. 7·3/15·2 cm., Fig. 8A) and an aorta that arose anteriorly and had a right-sided arch. The lungs were oligæmic and the pulmonary arteries were small.

The cardiogram with R and S waves of equal size in V4R and in V1 and with S waves only in V6 was thought to indicate some right ventricular preponderance, and the P waves were upright in the standard leads (Fig. 9). The diagnosis was pulmonary atresia.

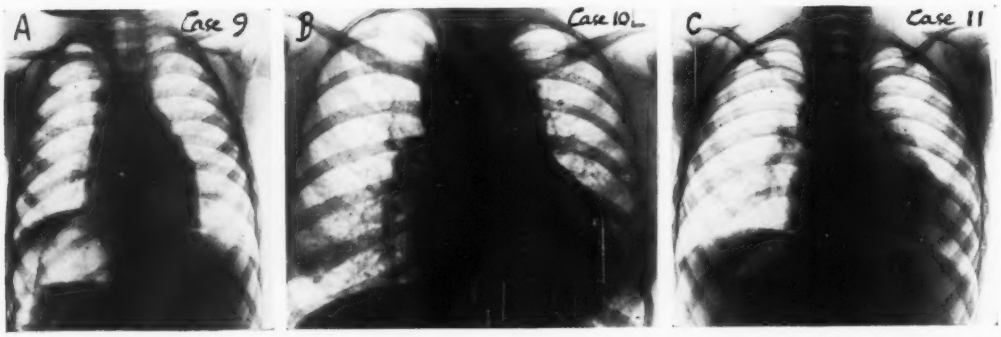

FIG. 8.—Teleradiograms from three cases with the venous atrium on the right. Those for Cases 7 and 8 have already been published. (A) Case 9, with a small central heart which was only slightly inclined to the left: the bilateral superior venæ cavæ do not show on the X-ray film. (B) Case 10 with a rather large heart and a broad pedicle that was partly due to bilateral superior venæ cavæ, both draining into the right atrium. (C) Case 11, with a rather large heart, a broad pedicle, and an unexplained indefinite shadow on the left. The aortic arch was right-sided in all these though it may be on either side when the venous atrium is on the right. All these three had bilateral superior venæ cavæ. The gas bubble in the stomach is well seen on the right in (A) and (C) and this was confirmed by barium in (B) though the liver was thought to be on both sides in this case.

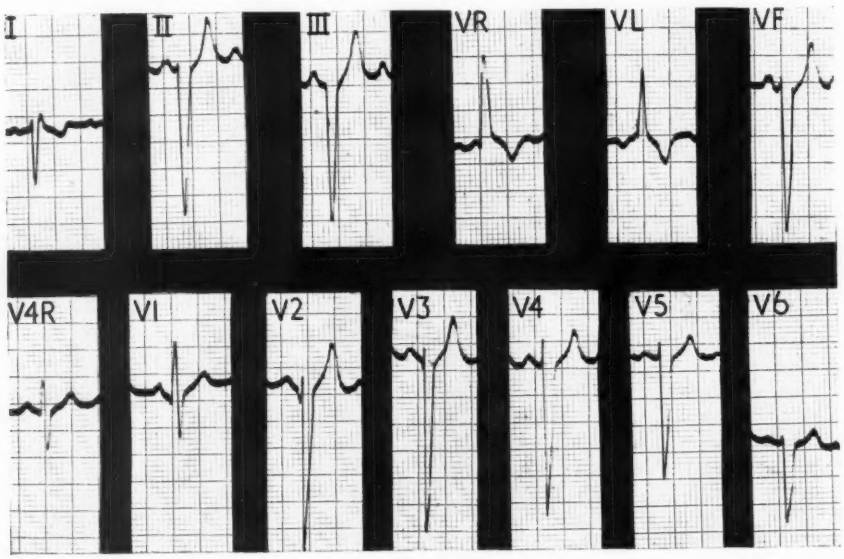

FIG. 9.—Case 9. Electrocardiogram showing upright PI. The standard leads show the sSS pattern and the chest leads show mainly S waves though R is about the same size as S from V4R to V1 and this, perhaps, indicates some right ventricular preponderance. Standardization 1 mV.=0·5 cm. in chest leads V4R to V6.

Angiocardiography was abandoned because of the severe fall of blood pressure when it was started. As he was getting worse, thoracotomy was decided on. The left superior vena cava seemed to empty into the left atrium, and the right superior vena cava was not seen, although in fact it was present. The left superior pulmonary vein seemed to pass behind the left atrium to join the right atrium so that the atria and venous system were thought to be transposed as the abdominal viscera were, and the apex of the heart pointed almost completely downwards. No pulmonary artery could be found for an anastomosis. The

findings at operation can not, therefore, give the detailed anatomy of these complex hearts. He had a stormy convalescence, including an attack of hemiplegia that was diagnosed as cortical thrombo-phlebitis, but recovered enough to go home and died rather suddenly three months later.

Necropsy. The heart was very central but just pointed to the left (Fig. 10). There were bilateral superior venæ cavæ and the left was joined by an azygos vein. The inferior vena cava entered the atrium below on the left and only a large hepatic vein entered on the right. Some hepatic veins also entered the inferior vena cava on the left. The atrium was large and single: above the ridge (see Fig. 11B) there was a primitive septum but below this the two sides communicated freely so that there was a single atrium. The two superior venæ cavæ entered the single atrium on either side of the primitive septum almost symmetrically but the right a little more obliquely and anteriorly: the left entered nearer to the entrance of the pulmonary veins (Fig. 11) and not through the coronary sinus. For some time no coronary sinus was found, but in the left side of the atrium some way below the entry of the left superior vena cava (B in Fig. 11B) there was a small opening, well-covered by a valve, leading to a vein that ran in the heart wall. The position suggested that it might have been a coronary sinus and, if so, it implies that the primitive venous system became obliterated in its middle part leaving the left superior vena cava patent above and a coronary sinus draining into the left side of the atrium below. The direction of flow through this vessel was, however, unusual for a coronary sinus.

There was a single bicuspid A-V valve with its longer axis lying transversely. There was also a single ventricle though there was a ridge that may have represented the septum. The only exit from the ventricle was through a rudimentary outflow chamber (Fig. 10) lying anterior and to the left and this could only be reached by the blood passing at the side of or through the fenestrations of the cusp of the A-V valve. At first no pulmonary trunk could be found because it was hidden directly behind the aorta, i.e. transposed. There was a moderately severe pulmonary valvular stenosis and some infundibular stenosis.

The pulmonary veins joined to form one from each lung and entered the single atrium above and on the left side, and the oxygenated blood passed through the single A-V valve to the common ventricle. The aorta and pulmonary trunk both arose from the rudimentary outflow chamber; the former was centrally placed and ascended vertically to arch to the right and the descending and abdominal aorta were also on the right.

Both lungs had three lobes. The stomach was on the right and the duodenum was also abnormal as it passed between the neck of a very large gall bladder and the liver. The liver appeared to be almost equally on both sides but the gall bladder was just to the right of the mid-line. No spleen was found. There was ante-mortem thrombosis of the right renal vein. The brain contained a fairly large area of softening in the left external capsule. This seemed to have followed from thrombosis and had been present for some months, possibly but not certainly before his operation. There was a much smaller area of softening in the right frontal pole that had probably been present only for days.

Case 10 (R.W., H126). This girl, aged 8, had been cyanosed from birth and was only able to walk a mile slowly. She had not squatted. There was moderate clubbing of the fingers.

There was a systolic murmur and a thrill in the third and fourth spaces in the left. There was no diastolic murmur, the pulmonary second sound was loud normal, and the blood pressure was 95/70. There was striking pulsation of the veins of the neck. Her heart was moderately enlarged (c.t.r. 61: m.t.d. 11/18 cm.) and was on the left (Fig. 8B); and later it was realized that the abdominal viscera were transposed. On screening the pedicle was very broad and both ventricles seemed large: the pulmonary arteries were easily seen and the lungs did not look oligæmic. The aortic arch was high and right-sided. The cardiogram showed right ventricular preponderance without right axis deviation and PI was large, broad, and upright. Her hæmoglobin was 122 per cent, the red cells 7·0 million, and the hæmatocrit 35 per cent.

Four years later, her condition and the physical signs were much the same. Although the liver seemed palpable on the right side, X-rays confirmed that the stomach was on the right and that the gall bladder was on the left so probably the liver was on both sides.

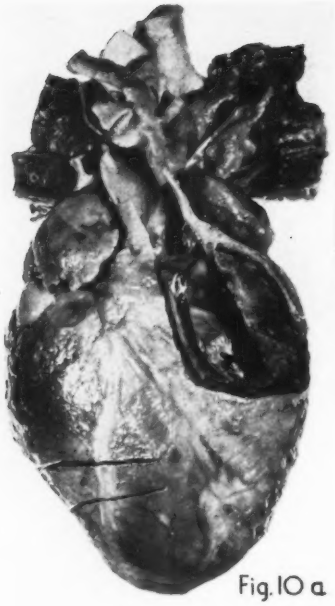

Fig. 10 a

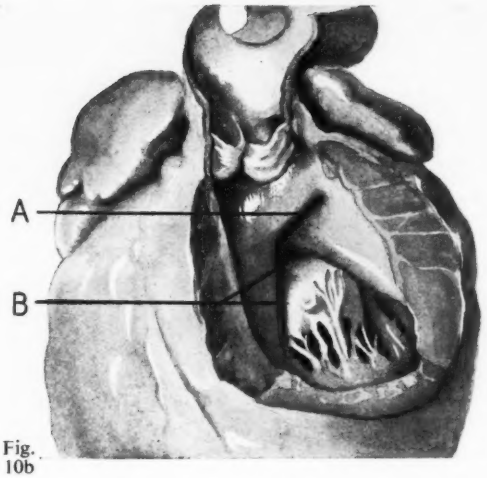

Fig. 10b

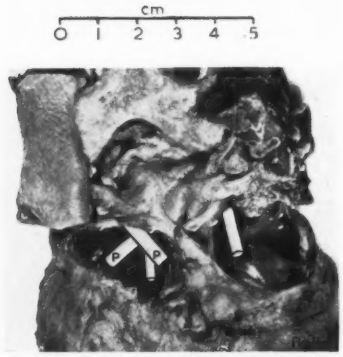

FIG. 10.—The heart of Case 9 from the front with the rudimentary outflow tract on the left and the central aorta opened. The small pulmonary trunk with a valvular and infundibular stenosis arose behind this. (A) Photograph of the heart. (B) Drawing of the outflow chamber. The aorta, which had three cusps, is seen opened. The small pulmonary trunk arose behind this, in the cleft marked A. The only way from the main cavity of the ventricle to this chamber was by the side of (marked B) and through the fenestrations of the anterior cusp of the A-V valve.

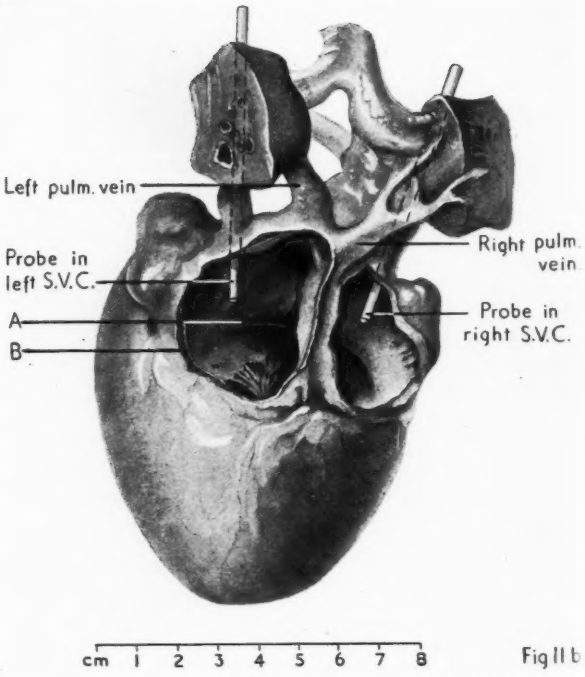

Fig 11 b

FIG. 11.—The heart of Case 9 from behind to show the single atrium. The hila of the lungs have been turned upward to display the pulmonary veins. These unite to form one vein from each lung both of which then enter the single atrium on the left side. Above the ridge marked A in the drawing there was a primitive septum but below this the two sides were in free communication with each other and joined the single ventricle through the single A-V valve. (A) Photograph of the heart. The crossed probes marked P are in the two pulmonary veins. The more vertical probes are in the two superior venæ cavæ. (B) Drawing of the heart. Probes have been passed down the right and left superior vanæ cavæ and pass respectively into the right and left sides of the common atrium.

Angiocardiography showed bilateral superior venæ cavæ and both entered the venous atrium on the right (Fig. 14C). Early opacification of the left atrium suggested an atrial septal defect. The aorta filled early at 2 sec. before the left ventricle and the pulmonary arteries filled slowly without much change in the density of the lungs.

On catheterization the pressure in the right ventricle (90/0 mg. Hg), and probably in the left also, was the same as in the systemic arteries. The pressure in the pulmonary trunk was much lower (4 mm.), confirming pulmonary stenosis. The O_2 saturations were difficult to understand: in the right atrium and ventricle (75–80%) they were higher than in the superior vena cava (66%) left ventricle? (68%), and brachial artery (64%), suggesting that a pulmonary vein entered the right atrium or that there was a left-to-right shunt through the atrial septal defect rather than the right-to-left shunt seen on angiocardiography. Only a partial diagnosis is possible. There are arterio-venous and veno-arterial shunts; the aorta over-rides or rises from the right ventricle; and there is also pulmonary stenosis, though at one time Eisenmenger's complex was suspected.

Case 11 (H.R., O116). This boy was under observation for five years. At the age of 3 years he only walked 100 yards: he had a high colour but no convincing cyanosis, though it had first been noticed at 3 months. When 5, there was a little cyanosis at rest and the fingers and toes showed early clubbing: he was able to attend an ordinary school When 8, he had improved further and could walk a mile at his own speed and cycled 6 miles to and from school.

There was a loud, widely-conducted systolic murmur and thrill in the pulmonary area. The pulmonary second sound was always loud and became louder, a short diastolic murmur was sometimes heard towards the apex, and the blood pressure was 90/60. The heart was on the left (Fig. 8C) and both ventricles seemed large (c.t.r. 60, 10·8/18·0 in 1948; 57, 12·6/22 in 1953): the aortic arch was right-sided. Pulsation was seen in the pulmonary arteries and at first beyond these. The pedicle was broad and there was an ill-defined shadow above the heart on the left gradually fading upwards, so that drainage of some pulmonary veins into a superior vena cava (Snellen and Albers, 1952; Gardner and Oram, 1953) was considered but seemed unlikely, and catheterization was unsuccessful. The cardiogram showed right ventricular preponderance with rather wide notched QRS complexes (0·10 sec.); PI was large and upright, PII inverted, and PIII generally inverted, but not in this record (Fig. 12). The hæmoglobin was 128 per cent and the red cell count 7·0 million with a hæmatocrit of 59 per cent. The stomach was under the right diaphragm and the liver was on the left.

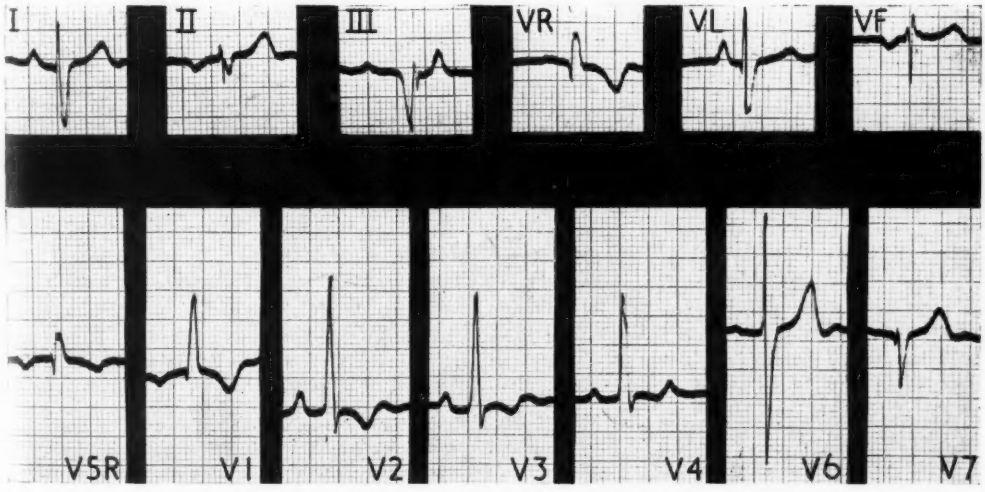

FIG. 12.—Case 11. Electrocardiogram showing upright PI and the more usual signs of right ventricular preponderance. Standardization 1 mV = 1·0 cm. in all leads.

TABLE II

CASES WITH THE VENOUS ATRIUM ON THE RIGHT

Case	Age and sex	Necropsy N Angico. A Catheter C Operation O	Inf. V.C.	Sup. ven. cav.		Pulm. veins	A.S.D.	V.S.D.	Aortic arch
				R.	L.				
Our Case 7	5M	NACO	Absent. Azygos to R. S.V.C.	R. side of single atrium	R. side through coron. sinus	Single atrium	++++*	++++*	L
Our Case 8	4F	NAO	RA	RA	—	LA	Slit-like PFO	++++*	L
Our Case 9	5M	NO	Left of single atrium	R. of single atrium	L. of single atrium	L. of single atrium	++++*	++++*	R
Doliopoulos and Maillet (1952) Case, 1	4F	NA	RA	RA	—	LA	+++	++++*	R
Doliopoulos and Maillet (1952), Case 3	1F	N	LA	RA	—	LA	++	++	L
Young and Griswold (1951) Case 2	10M	NAO	R. side of single atrium	R. side of single atrium	To R. S.V.C. by innominate	To L. S.V.C.	++++*	++	R
Robinson and Garfinkle (1950)	6daysM	N	RA	RA	Abs.	LA	+	++	?L
Tanner-Cain and Crump (1951)	3daysF	N	?	?	?	?	No	No	?

* ++++ denotes such a large defect that it was a single chamber.

Angiocardiography showed a superior vena cava and a venous atrium on the right (Fig. 14D) and suggested that a pulmonary vein entered the right atrium. The diodone passed from the right to the left atrium so that all the heart was quickly opacified. The aorta was large and arched to the right; it arose well over to the left but it was difficult to say from which ventricle. The pulmonary arteries filled slowly—less well than was expected from radioscopy—and too little blood passed through the lungs to opacify the left atrium again or the unusual shadow to the left of the aorta.

He was thought to have an atrial septal defect, at first with a shunt that was mainly left-to-right; cyanosis then appeared at rest and pulsation in the pulmonary arteries decreased as the shunt became reversed. The increasingly loud pulmonary second sound suggests that a rise of the pulmonary blood pressure was responsible for this.

OTHER CASES WITH P UPRIGHT IN LEAD I

Three of our cases and four others—Case 2 of Hardy (1948), Case 2 of Thompson (1950), Case 5 of Doliopoulos and Maillet (1952), and probably Case 8 of Young and Griswold (1951)—belong to this group because of the upright PI. They are not included in Table III or used in the discussion because special investigations were not made or were too incomplete. Short notes of our three cases follow.

Case 12 (R.T., O014). He was seen when a year old. He was never able to walk and was cyanosed from birth, with early clubbing of the fingers. From 2 years onwards he had several attacks of intense dyspnœa, prostration, pallor, and coughing, and he died suddenly at the age of 3 in one of these attacks.

A soft systolic murmur was heard in the pulmonary area and the second sound was normal. The heart was large and sabot-shaped (c.t.r. 60: 9·7/16 cm.) and the lungs looked oligæmic with bronchial arteries carrying the main blood supply. The aortic arch was probably right-sided. The cardiogram showed right

SIDE AS NORMALLY (ALL WITH NECROPSIES)

Origin of aorta	Origin of pulm. trunk	Pulm. orifice	Lungs	PI	EC	Remarks
From R. of single V.	Dimple just L. of aorta	Pulm. atresia	Oligæmic	Upr.†	RVP	Bilocular heart. Pulm. atresia. Lungs supplied through PDA
From R. of single V.	L. of aorta	PVS	Oligæmic	Upr.	RVP	Mitral atresia. Blood reached single ventricle through PFO and RA.
Centrally from single V.	Posterior to aorta	PVS	Oligæmic	Upr.	Some RVP	Heart almost bilocular and very central
Over-riding RV. Almost single V.	L. of aorta	Pulm.	Oligæmic	Upr.	RVP	Single ventricle. Large ASD. Pulmonary atresia. PDA.
From RV.	From RV posterior to aorta	?Normal	?Normal ?Oligæmic	Flat	RAD	ASD, VSD and aorta from RV with or without pulm. stenosis
Over-riding, mainly RV	From LV	Pulm. stenosis	Oligæmic	—	RVP	Single atruim. Anomalous pulm. veins. Pulm. stenosis
From RV	From LV	Normal	?Congested	—	No EC	ASD, VSD, PDA, Transposition
?From LV	?From RV	Normal	?	?	?	

† Inverted PII and PIII. This patient had duodenal atresia.

ventricular preponderance with an upright PI. The hæmoglobin was 110 per cent, the red cell count 7·3 million. The gastric air bubble was under the right diaphragm, but the liver was probably on both sides.

A tentative diagnosis of pulmonary atresia with bronchial artery blood supply to the lungs was made. There was no necropsy.

Case 13 (J.L., O823). She was cyanosed from birth and severely so with marked clubbing of the fingers when she was seen at the age of 4 years. Her physique was very poor and she was unable to stand.

A trivial systolic murmur in the pulmonary area was followed by a double second sound, and there was a triple rhythm at the apex. The heart was large (c.t.r. 65: m.t.d. 10·1/15·5 cm.), the vascular pedicle was very broad, and the aortic arch was right-sided. The lungs were oligæmic. The stomach was seen under the right diaphragm, but the liver may have been partly on both sides. The cardiogram showed right ventricular preponderance, and the P waves were upright in lead I and deeply inverted in leads II and III. The hæmoglobin was 120 per cent.

The findings, with the exception of the double second sound, were consistent with pulmonary atresia. She died a year later in a fit while her mother was bathing her, having got much worse after measles some months before and having other convulsive fits in the weeks before her death: there was no necropsy.

Case 14 (N.R., P222). A fit man, now aged 32, was the Case 1 of Forgacs (1947). We need only add that he has got on well during the subsequent six years and his heart is no larger (c.t.r. 54: m.t.d. 15·7/29 cm.). He has put on too much weight and is breathless playing tennis singles or running upstairs but not otherwise. He has consistently shown left ventricular hypertrophy on radioscopy and cardiography and the average of many readings of his blood pressure is 145/75. A faint aortic diastolic murmur has been heard at some visits but not regularly. The aortic arch is left-sided. He has always shown an upright PI and inverted PII and PIII.

We do not now accept the explanation that was then suggested. He probably has aortic incompetence and this may be due to bicuspid aortic valves. This, the most natural explanation, was rejected in 1946 because no aortic diastolic murmur had then been heard.

TABLE III

CASES WITH THE VENOUS ATRIUM ON THE

Case	Age and sex	Necropsy N Angioc. A Catheter C Operation O	Inf. V.C.	Sup. ven. cav.		Pulm. veins	A.S.D.	V.S.D.	Aortic arch
				R.	L.				
Our Case 10	8F	AC	?RA	RA	RA through cor. sinus	?	++	?+	R
Our Case 11	8M	A(C)	?RA	RA	—	?	++	?	R
Doliopoulos and Maillet (1952), Case 2	3F	A	?RA	RA	?Abs.	?LA	?	++	L
Young and Griswold, Case 3	15m.F	AO	?RA	Abs.	RA through cor. sinus	?	++	?+*	L
Young and Griswold, Case 4	4M	ACO	?	RA	LA	LA but one PV to Rt. SVC	+	?++	R
Young and Griswold, Case 5	8M	ACO	To L. S.V.C.‡	?Abs.	RA through cor. sinus	LA	++	?+*	R
Young and Griswold, Case 6	9M	ACO	?RA	RA	RA through cor. sinus §	?RA †	+ †	+*	L
Young and Griswold, Case 7	6F	ACO	?RA	RA	?LA ?RA through cor. sinus	?RA†	+ †	?*	R
Del Carril *et al.* (1949)	21m.F	AC	RA	RA	RA through cor. sinus	?	+	?	R

* Only evidence is that aorta was thought to be over-riding.
† At least one pulm. vein to RA or left-to-right shunt through A.S.D.
‡ I.V.C. probably absent with large azygos vein to left S.V.C.
§ Personal communication from Dr. Taussig. Single atrium not excluded in this or in Young and Griswold, Case 3.

DISCUSSION OF GROUP WITH THE VENOUS ATRIUM ON THE LEFT

Five of our cases belong to this group but very few of the others reported so that there are only seven in all and only two with necropsies (see Table I). These seven have certain features in common: the superior and inferior venæ cavæ are on the left, and so far as we know on this side only, and enter a venous atrium on the left; the pulmonary veins enter the right atrium; and the aortic arch is right-sided. If the structure of the heart were otherwise normal and the aorta arose from the left ventricle, the venous blood would be returned to the systemic circulation and the patient could not survive. If the aorta and pulmonary trunk were transposed without any other abnormalities the circulation would be functionally normal.

In our Case 1 where the anatomical facts are known fully, the systemic veins entered a left (venous) atrium which had the general appearance and shape of a normal right atrium, and joined a left ventricle through a valve that had three cusps. The pulmonary veins entered a right (arterial) atrium, which had the general appearance and shape of a normal left atrium, and communicated with a right (arterial) ventricle through a valve that had two cusps. The aorta arose from this and not from the left ventricle. If the pulmonary trunk had arisen directly from the left ventricle the circulation, being a mirror image of the normal, would have been functionally normal, but there was pulmonary stenosis and a large ventricular septal defect and the pulmonary trunk over-rode this. There must also have been a large left-to-right (veno-arterial) shunt through the ventricular septal defect to the aorta to account for the severe anoxæmia: presumably the pressure was higher on the left side because of the pulmonary stenosis.

The only other case with a necropsy (Young and Griswold, Case 1) agrees fully with this in

RIGHT SIDE AS NORMALLY (NO NECROPSIES)

Origin of aorta	Origin of pulm. trunk	Pulm. orifice	Lungs	EC	PI	Remarks
?From RV	??LV	Pulm. stenosis	?	Some RVP	Upr.	Pulmonary stenosis
?	?	?Pulm. stenosis	?Pleonæmic and later oligæmic	RVP	Upr.	ASD and ?pulmonary hypertension
Over-riding RV	?	Slight P.S.	?Oligæmic	RVP	Upr.	VSD and over-riding aorta with slight pulm. st.
Over-riding RV	?	?P.S.	Oligæmic	RAD	Inv. and Upr.	ASD. ?Fallot Died 6/12 after operation
?Over-riding RV	?RV	?P.S.	Oligæmic	RAD	Inv. and Upr.	?Fallot Anomalous pulm. veins
Over-riding RV	?	?P.S.	Oligæmic	LVP	Upr.	ASD. ?Fallot
?Over-riding RV	?Posterior to aorta	?P.S.	Oligæmic	RAD	—	?Fallot
?Over-riding RV	RV	P.S.	Oligæmic	RAD	Inv. or biphasic	Pulmonary stenosis
?	?	?	?	RVP	Upr.	Diagnosis uncertain

the structure of the veins, atria, and ventricles but there was pulmonary atresia instead of stenosis and the aorta was mainly, instead of entirely, from the right ventricle. Unfortunately, the report does not say which A-V valve had two cusps and which had three cusps and the case of Robinson and Garfinkle (1950) (see Table II) does not help because both A-V valves had two cusps.

In the other five the arrangement of the systemic veins and atria was the same as in the two with necropsies (see Fig. 13). The aorta received venous blood, but it was not certain that it arose from or over-rode the right ventricle because there was a large left-to-right (veno-arterial) shunt through an atrial septal defect: this means that the pressure must have been higher on the left (venous) side, probably because of pulmonary stenosis.

In Case 4, who was very cyanotic and disabled, the aorta seemed to arise mainly from the left (venous) ventricle (see figures for O_2 percentage) and the catheter took this course, and in Case 5

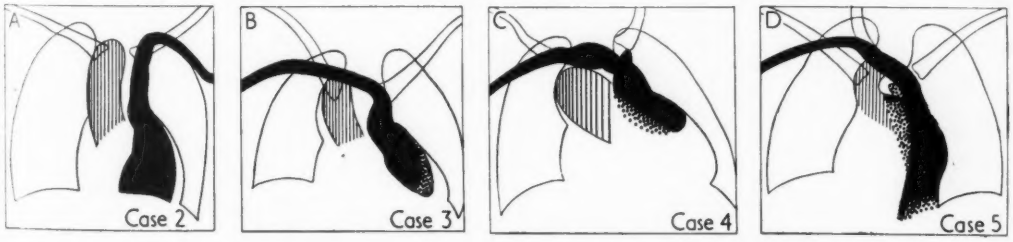

FIG. 13.—Diagrams of the angiocardiograms from four cases where the venous atrium is on the left. These are taken from tracings of several angiocardiograms, so that the part filling first is shown in dark black and in some cases the spread beyond by dotted black. The aorta is shown from later records by hatched lines. In (B) and (C) the left atrium seems more in the normal position of the left atrium and in (A) and (D) more in the mirror-image position of a right atrium.

the angiocardiogram favoured an aorta from the left ventricle; but in Case 3 who was less disabled the figures for the O_2 saturation suggested that the aorta arose from the right (arterial) ventricle, and in Case 2 it was uncertain. In all these four there was an atrial septal defect and this was probably the site of the left-to-right (veno-arterial) shunt. In several of these cases transposition of the aorta and pulmonary trunk seems to be the method used to overcome the abnormal venous return: it often fails because pulmonary stenosis produces a large veno-arterial shunt through a septal defect.

Discussion of group with the Venous Atrium on the Right as Normally

When the systemic veins and venous atrium remain on the right as normally, there is no need teleologically for transposition of the great vessels and, if the aorta arose from the left ventricle, the circulation should be normal. This, however, is most unusual and only one of our eight (Case 14) is acyanotic and without much disability. The cyanosis and disability of the others may be entirely due to the associated defects but at least it means that there is some fundamental fault in development that makes these the rule when there is lævocardia and transposition of the abdominal viscera.

In discussing the full diagnosis only the cases with necropsies can be used and, omitting the one of Tanner-Cain (1951) for the reasons given, this leaves 7 with the venous atrium on the right (Table II). All these had multiple defects that were more than enough to account for their cyanosis and disability. Three or four, if we include our Case 8 where all the blood from the left atrium had to pass to the right atrium to reach the ventricle, had a single atrium and the other three an atrial septal defect. Four had a single ventricle and the other three a ventricular septal defect. In addition there was pulmonary atresia in two and pulmonary stenosis in three at least.

The venous blood from the systemic veins entered the right atrium or the right side of a single atrium (see Fig. 14), except that the inferior vena cava entered the left atrium in Case 3 of Doliopoulos and Maillet and the left side of a single atrium in our Case 9.

The pulmonary veins entered the left atrium or the left side of a single atrium in all these except one (Case 2 of Young and Griswold), where they passed via the left superior vena cava and the innominate vein to the right side of a single atrium.

In the three cases where there was not a single ventricle, the aorta was transposed and arose from the right ventricle in two (including the only one where the pulmonary trunk was not transposed) and mainly from the right but over-riding the left in one (Case 2 of Young and Griswold). The pulmonary trunk arose from the right ventricle in one (Case 3 of Doliopoulos and Maillet) but was transposed and arose from the left ventricle in two. There was partial transposition in most of those with a single ventricle, but this prevents transposition having its usual functional significance and makes it more difficult to say from which ventricle the aorta would have arisen. Transposition, complete or partial, was therefore an important cause of the cyanosis and disability

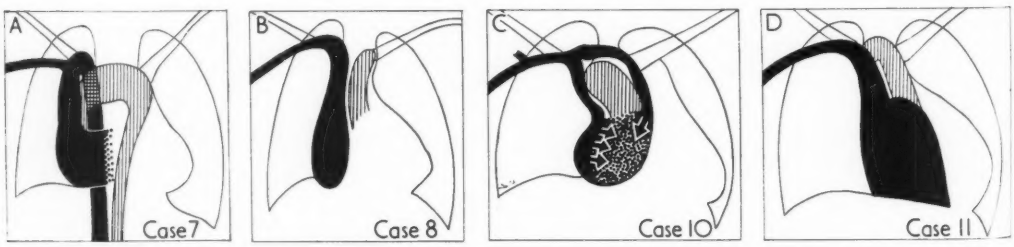

Fig. 14.—Diagrams of the angiocardiograms from four cases where the venous atrium is on the right. For explanation see Fig. 13. In (A) the angiocardiogram was done from below through the azygos vein and the descending aorta in marked, as well as the arch, to show their relationship. In (C) the filling took place through bilateral venæ cavæ and the left was thought to enter the right atrium through the coronary sinus.

in these patients and with the other defects described was more than enough to explain them. All these defects, of course, often occur without transposition of the abdominal viscera.

The Venæ Cavæ. In addition to the 7 cases with necropsies (Table II) the 9 that had angiocardiography and often cardiac catheterization (Table III) can be used for this part of the discussion. We have included all these where a right-sided superior vena cava drained into a right atrium, even if the left superior vena cava was thought to drain into the left side. There was a right superior vena cava (S.V.C.) in all the cases with necropsy and in at least 7 of the 9 others: in all these it entered the right atrium or the right side of a single atrium. In the remaining 2 where there was no proof of a right S.V.C., the left S.V.C. entered the right atrium through the coronary sinus.

There was a left S.V.C. as well as a right S.V.C. in at least 8 cases, while in the previous group with the venous atrium on the left there was never proved to be one on both sides. In 4 of the 8 it drained into the coronary sinus and so reached the right atrium or in one instance the right side of a single atrium. In one instance it received the pulmonary veins and drained into the right S.V.C. (Case 2, Young and Griswold). In another (our Case 9 with necropsy) it went directly into the left side of a common atrium. In one or two, neither supported by necropsy proof (Young and Griswold, Case 4 and less certainly Case 7), it was thought to enter the left atrium. Bilateral venæ cavæ are perhaps even more common than would appear from these figures, for unless both sides are explored at angiocardiography and catheterization (and information about this is not always available) one of these veins may not be demonstrated.

The inferior vena cava presumably went into the right atrium in most of these cases but there was generally no proof of this unless there was a necropsy. In one, however, it went into the left atrium (Case 2, Doliopoulos and Maillet) and in our Case 9 into the left side of a single atrium. In our Case 7 it was absent and the lower half of the body was drained by the azygos vein which entered the right S.V.C. This was also probable in Case 5 of Young and Griswold where a large vein, probably the azygos vein, was seen entering the left S.V.C.

The Pulmonary Veins. In all the cases with necropsy the pulmonary veins drained into the left atrium or the left side of a single atrium, except in the one just mentioned where they drained into a left superior vena cava (Case 2, Young and Griswold). Probably this was also true in the cases who are living but there was less direct evidence except in Cases 4 and 5 of Young and Griswold and in the former one pulmonary vein drained into the right superior vena cava and so into the right atrium. In their Cases 6 and 7, either some pulmonary veins must have entered the right atrium or there must have been a left-to-right shunt through an atrial septal defect.

The Aortic Arch. In the previous group with the venous atrium on the left the aortic arch was always right-sided, but the reverse is not true. When the venous atrium was on the right, the aortic arch was left-sided in 7 and right-sided in 9 cases. The side of the aortic arch was not constantly correlated with the side of the superior vena cava but when there was only a right-sided superior vena cava the aortic arch was more often left-sided (4 of 6 cases) and when there were bilateral superior venæ cavæ the aortic arch was more often right-sided (6 of 8 cases). In the two cases where the only known superior vena cava was on the left but entered the right atrium through the coronary sinus, the aortic arch was right-sided in one and left-sided in one.

Atrial and Ventricular Septal Defects

Septal defects are common in both groups so they are combined in this section. A defect of the atrial septum, varying from a patent foramen ovale (3 cases) to a common atrium (3 cases), was present in 19 of the 24 cases and was thought probable in at least 2 others.

In the 10 cases that came to necropsy, a single ventricle was found in 4, a ventricular septal defect in 5, and no communication between the ventricle in 1 only. A ventricular septal defect was thought to be present in at least 7 of the other 10 cases. Except for the infant described by Tanner-Cain and Crump (1951) every case with necropsy control had a communication between

the atria and between the ventricles, and this seemed likely in many of the others as well. Labesse (1952) has mentioned the frequent occurrence of atrial and ventricular septal defects and that the superior venæ cavæ may be bilateral.

It is difficult to be certain about the arrangement of the ventricles and of the great arteries in cases investigated by clinical methods alone. In the six necropsied cases with both ventricles present the aorta originated from the right ventricle in three, mainly from the right but over-riding the septum in two, and from the left ventricle in one.

Transposition of the Abdominal Viscera

In all these cases the abdominal viscera were thought to be transposed but the transposition was not always complete. In the four with necropsies it was complete in Case 1 but in the others the liver was rather central (Case 7) or on both sides (Case 8 with the gall bladder on the left and Case 9 with it just on the right). No spleen was found in Cases 8 and 9 and in Case 7 the spleen had four lobes. In some of the cases investigated clinically the liver was thought to be on both sides (Cases 5 and 10) but in the latter the gall bladder was on the left.

The Blood Supply to the Lungs

The congenital heart disease is usually serious and, with two exceptions, all the cases reviewed were cyanosed. The cyanosis is generally striking and the disability severe. Death at an early age is likely, since only three of these patients were over 10 years of age at the time of examination.

The adequacy of the blood supply of the lungs is of interest from the point of view of surgical treatment. Pulmonary stenosis was found in 4 and pulmonary atresia in 3 of the 10 cases with necropsy, and the pulmonary blood flow was thought to be reduced in 16 of the 24 with necropsy or full investigation. Probably, therefore, most of these patients can be helped by operation in spite of the complex abnormalities.

The only series dealing with the surgical results is Young and Griswold's (1951), on each of whose eight cases a Blalock operation had been performed: three died within seven months of the operation, but the other five were much improved. Five of our patients have had operations: one (Case 4) had a subclavian-pulmonary anastomosis and two years later was a good deal better; two died soon after an anastomosis and in two, one of whom died later, no anastomosis was possible because the pulmonary artery could not be found.

The Relationship of the Direction of PI to the Side of the Venous Atrium

As in most cyanotic congenital heart disease, right ventricular preponderance is usual in the electrocardiogram. It was found in 22 cases, while left ventricular preponderance was found in four or five only.

Campbell and Reynolds (1952), from a study of these 14 cases and 23 others with complete heterotaxy or isolated dextrocardia, concluded that inversion of PI generally indicates a superior vena cava and a venous atrium on the left side of the heart. PI was inverted (as a rule) in 6 of our 14 cases (Fig. 2, 3, and 4) and in all the 5 where the information was available a left-sided superior vena cava entered a venous atrium on the left (Fig. 13). PI was upright (as a rule) in 8 of our 14 cases (Fig. 9 and 12) and in all the 5 where the information was available a right-sided superior vena cava entered a venous atrium on the right or the right side of a single atrium (Fig. 14).

Cases 1 and 2 of Doliopoulos *et al.* (1952) with an upright PI and Case 4 with an inverted PI support this view. In their Case 5 there was no comment on the position of the venous atrium so probably it was normal and PI was upright, and in their Case 4, PI was isoelectric so it does not help. Nor does the case of Del Carril *et al.* (1949) help for they state that PI was inverted but that a second record showed this was due to nodal rhythm.

Young and Griswold (1951) do not mention the P waves but Dr. Helen Taussig has kindly

given us some information. No notes are available of Cases 1, 2, and 6 and PI was sometimes inverted and sometimes upright in Cases 3 and 4: these five cannot therefore help us. In Cases 5 and 7 the venous atrium was on the right and the former supported our theory by having upright P waves in lead I but the latter opposed it as they were negative or possibly biphasic. In the reported cases where the information is available there were, therefore, four in favour of and one against the theory that the shape of PI indicates the side of the venous atrium.

Summary

We have described 14 cases of congenital heart disease with transposition of the abdominal viscera but with lævocardia, and have compared them with 19 similar cases that have been reported recently. In a lesion of such complexity, only the 10 with necropsies can provide full details of the anatomical changes; but including these there are 10 of our cases and 14 others that have been investigated, generally by angiocardiography and by cardiac catheterization, and these 24 have been analysed and used as far as possible for discussion of the changes.

They fall into two groups (*a*) those where the superior vena cava and venous atrium are on the left, i.e. transposed with the abdominal viscera, and (*b*) those where the venous atrium is on the right as normally, but where the cyanosis and disability are due to the associated defects. The conclusion of Forgacs (1947) that congenital heart disease is the rule in this type of heterotaxy is confirmed, as is the transposition of the atria in the former group, but the assumption that transposition of the atria is the fundamental cause of the other defects is no longer tenable.

In those with the venous atrium transposed to the left, the P wave in lead I is inverted and there is generally a single superior vena cava, also transposed to the left, and a right-sided aortic arch. As a rule, the aorta and pulmonary trunk are partially or completely transposed, but this adaptation, which should be effective, is rendered ineffective by the presence of septal defects and pulmonary stenosis or atresia.

In those with the venous atrium on the right as normally—about half our cases but much more than half of the total number—the P wave in lead I is generally upright and there is often a superior vena cava on both sides, the left generally entering the right atrium through the coronary sinus. The aortic arch may be on either side. As in the first group, the aorta and pulmonary trunk are often partially or completely transposed and there are atrial and ventricular septal defects, often indeed a single atrium or single ventricle, and generally pulmonary stenosis or atresia.

In view of the different arrangement of the atria in these two groups, a different pattern of the other defects in the heart might be expected. They are, however, found to be very similar: atrial and ventricular septal defects, partial or complete transposition, and pulmonary stenosis or atresia are often found in both. Evidently the failure to decide on which side the development is to take place causes fundamental difficulties in the complex processes of growth and rotation that divide the heart into its two sides and bring the aortic and pulmonary rings opposite the correct ventricle.

A Blalock-Taussig operation should be helpful in most cases of both groups though perhaps the result cannot be expected to be as good as in uncomplicated cases of Fallot's tetralogy. If the patient is sufficiently disabled it can be advised whenever the blood flow to the lungs is diminished and suitable pulmonary arteries are present. In the cases reported by Young and Griswold (1951) the results have been good but out experience so far has been less fortunate.

We should like to thank the registrars of the National Heart Hospital for the investigations of Case 4, and Dr. D. Deuchar for the findings at cardiac catheterization, and Dr. T. H. Hills for the angiocardiograms of the other cases. We are grateful to Miss M. Waldron of the Department of Medical Illustration for the drawings and Mr. C. Engel of the Photographic Department, Guy's Hospital, for the photographs."

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PATENT DUCTUS ARTERIOSUS WITH PULMONARY HYPERTENSION

BY

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In most cases of patent ductus arteriosus the diagnosis is readily made on recognition of the typical murmur. In some, however, the continuous murmur is lacking, and a systolic murmur only, of variable loudness, is heard at the pulmonary area. This is not uncommon in infants and young children, who may later develop the characteristic murmur (Gilchrist, 1945). Occasionally the continuous murmur is absent in adults in whom patency of the ductus is found subsequently at autopsy: in such cases the state of the pulmonary arteries and the presence of right ventricular hypertrophy may indicate that the pulmonary arterial pressure was much raised in life (Holman, 1925; Keys and Shapiro, 1943 (Case 3); Chapman, 1944; Douglas *et al.*, 1947 ; Ulrich, 1947). As a result, the pressure gradient between the aorta and the pulmonary artery may be so diminished that the blood flow along the ductus is insufficient to set up a continuous murmur. In extreme examples the pressure in the pulmonary artery may exceed that in the aorta, causing a reversal of the usual left to right shunt (Johnson *et al.*, 1950; Campbell and Hudson, 1951; Dammann *et al.*, 1953).

Three cases of patent ductus arteriosus complicated by severe pulmonary hypertension are presented here. The diagnosis was made in each on cardiac catheterization. In two, pulmonary hypertension caused reversal of the shunt; in the third the shunt was not reversed, but there was, in addition, coarctation of the aorta.

Case 1. A woman, aged 27, had dyspnœa on effort for many years. At the age of 5 she had had chorea, but no cardiac abnormality was ever noted in childhood. In the past two years dyspnœa had become worse, and she developed slight cyanosis. On examination no colour difference was seen between the hands and feet, and there was no clubbing of the fingers or toes. The apex beat was not displaced; the second sound was accentuated and closely split at the pulmonary area, where a faint systolic murmur was also heard. Radioscopy showed enlargement of the right atrium and ventricle, and the main and right pulmonary arteries were enlarged and pulsating. The electrocardiogram showed marked right ventricular hypertrophy.

On cardiac catheterization the tip of the catheter passed readily from the pulmonary artery into the aorta in the position typical of passage through a ductus arteriosus (Bouchard *et al.*, 1951). Pressures (capacitance manometer) and blood oxygen content and capacity (Haldane) were as follows:

	Pressure mm./Hg	*Oxygen content ml./l.*	*Oxygen satn. percentage*
Superior vena cava	—	126	58
Inferior vena cava	—	104	48
Right atrium (2 positions)	7	115	53
Right ventricle (2 positions)	150/5	115	53
Right pulmonary artery	150/88	115	53
Descending aorta	130/92	163	75
Descending aorta (after breathing O_2 for 5 min.)	130/92	173	79
Left radial artery (5 days later)	—	201	92
Right femoral artery (5 days later)	140/94	163	75

Blood oxygen capacity: 218 ml./l. Oxygen consumption: 228 ml./min.
Pulmonary blood flow: 2·65 l./min. Total pulmonary resistance: 3300 dynes. sec. cm^{-5}.

There was, therefore, a shunt from the pulmonary artery into the aorta, for pulmonary arterial pressure exceeded that in the aorta, and a reduced oxygen saturation was found in the descending aorta and femoral artery, and was not fully corrected by breathing oxygen.

Case 2. A girl, aged 9, had always had some dyspnœa on effort. She was able to lead a normal life, although strenuous effort caused considerable dyspnœa and cyanosis. At rest in bed, cyanosis was visible in the feet but not in the hands, and there was clubbing of the toes but not of the fingers. The apex beat was not displaced; the second sound was loud and closely split at the pulmonary area, and a moderately loud systolic murmur was heard all over the præcordium. Radioscopy showed enlargement of the right atrium and ventricle, and of the pulmonary arteries, with pulsation of the main branches. The cardiogram showed right ventricular hypertrophy.

On cardiac catheterization the tip of the catheter passed from the pulmonary artery into the aorta in the position typical of passage through a ductus arteriosus. The pressure in the right ventricle was 120/6, in the left pulmonary artery 120/70, and in the aorta 120/84 to 130/90 mm./Hg.

On another occasion, under nitrous oxide and oxygen anæsthesia, blood samples were withdrawn simultaneously from the carotid and femoral arteries. Oxygen content was estimated by van Slyke's method, the results being uninfluenced by the presence in the blood of nitrous oxide. The O_2 saturation in the carotid artery was 68 per cent and in the femoral artery 52 per cent.

Thus, on cardiac catheterization, the aortic and pulmonary arterial pressures were approximately equal, but at other times the colour of the limbs and analysis of arterial blood samples showed that blood flowed from the pulmonary artery into the aorta.

Case 3. A man, aged 25, was noted to have a heart murmur at the age of 10, but had no symptoms until he developed dyspnœa on effort at the age of 14. A year later he began to have cramp-like pains in the thigh muscles on effort. Systemic hypertension was found at the age of 23, when a diagnosis of coarctation of the aorta was made. On examination no cyanosis or clubbing of the fingers was seen, but his hæmoglobin level was 130 per cent. There was an asymmetrical shallow depression of the sternum and adjoining ribs on the right side. The apex beat was in the fifth intercostal space one inch beyond the midclavicular line. The pulmonary second sound was accentuated but not widely split; there was a moderately loud systolic murmur at the apex, and a high pitched early diastolic murmur at the left sternal border. The femoral pulses were palpable but poor compared with the brachial pulses; blood pressure in the arm, by sphygmomanometer, was 180/90, and in the leg systolic pressure was 120 mm./Hg.

Radioscopy showed considerable cardiac enlargement, involving both ventricles; the pulmonary artery was greatly enlarged, and it and its main branches were pulsating. A radiogram showed calcification in the wall of the main pulmonary artery; there was no rib notching (Fig. 1). The cardiogram showed right ventricular hypertrophy and incomplete right bundle branch block (Fig. 3).

On cardiac catheterization the catheter was passed along a patent ductus arteriosus into the aorta (Fig. 2), and the findings were as follows:

	Pressure mm./Hg	*Oxygen content ml./l.*	*Oxygen satn. percentage*
Right atrium	10/0	134	59
Right ventricle (high)	160/5	160	71
Pulmonary artery	160/70	160	71
" Pulmonary capillary "	12	—	—
Aorta, descending	120/90	217	96
Left femoral artery	120/85	217	96
Right brachial artery	160/80	216	95

Blood oxygen capacity: 227 ml./l. Oxygen consumption: 394 ml./min.
Pulmonary blood flow: 6·9 l./min. Systemic blood flow: 4·7 l./min.
Pulmonary arteriolar resistance 1135 dynes. sec. cm.$^{-5}$ and total pulmonary resistance 1275 dynes. sec. cm.$^{-5}$

As the catheter tip was withdrawn from the aorta back into the pulmonary artery the recorded pressure rose suddenly. Although the pulmonary arterial pressure clearly exceeded that in the descending aorta there was no evidence of a shunt from the pulmonary artery into the aorta. From this it was inferred that the ductus entered the aorta at or proximal to the site of coarctation, i.e. it entered that part of the aorta where the pressure was high. There evidently was a shunt from the aorta into the pulmonary artery, for the pulmonary arterial blood was richer in oxygen than that from the right atrium. The right ventricular blood sample, which was withdrawn from a point in the outflow tract, was similarly enriched as compared with right atrial blood, suggesting that the pulmonary valve was incompetent. The coarctation was

obviously not severe, for the catheter had passed through it into the descending aorta, and this explained the absence of rib notching.

At thoracotomy (Mr. R. Belsey) a greatly dilated and tense pulmonary artery was found, with a patent ductus arteriosus about 3 cm. in length and 0·5 cm. in external diameter, entering the aorta at the site of coarctation. Direct pressure records from the aorta and pulmonary artery gave results similar to those obtained at cardiac catheterization, though all were now somewhat lower. Temporary occlusion of the

FIG. 1.—Case 3. Patent ductus, coarctation of aorta, and pulmonary hypertension. Teleradiogram showing generalized cardiac enlargement. A line of calcification is seen in the wall of the main pulmonary atrery; this and the right pulmonary artery are much dilated, and were seen to pulsate on radioscopy. The aortic knuckle is small and there is no rib notching.

FIG. 2.—Case 3. The cardiac catheter has passed *via* the patent ductus through the coarctation into the descending aorta.

ductus caused a slight rise in pressure in the proximal aorta, but no significant fall in the pulmonary arterial pressure. Both the ductus and the coarctation were left *in situ*. Biopsy of the lung was performed, and microscopy showed great hypertrophy of the pulmonary arterial and arteriolar walls. In the arterial walls there was an increase in the muscle and elastic tissue in the media, with occasional small raised plaques of fibro-elastic tissue in the intima. The arteriolar walls showed hypertrophy of the media and thickening of the intima without plaque formation (Fig. 4).

DISCUSSION

Two main problems now arise. First, what is the connection, if any, between patency of the ductus arteriosus and pulmonary hypertension? and secondly, should the ductus be ligated?

Pulmonary arterial pressure is increased to a variable degree in the presence of a patent ductus. Usually this increase is small and appears to be due merely to the increased pulmonary blood flow, for in most cases of patent ductus arteriosus the pulmonary vascular resistance is normal or reduced (Dexter *et al.*, 1950; Wood, 1950; Wood, 1952). The patients described above were unusual in that their pulmonary arterial pressure and pulmonary vascular resistances were both greatly raised. There are few reports on the late effects of closure of the ductus upon pulmonary hypertension, but

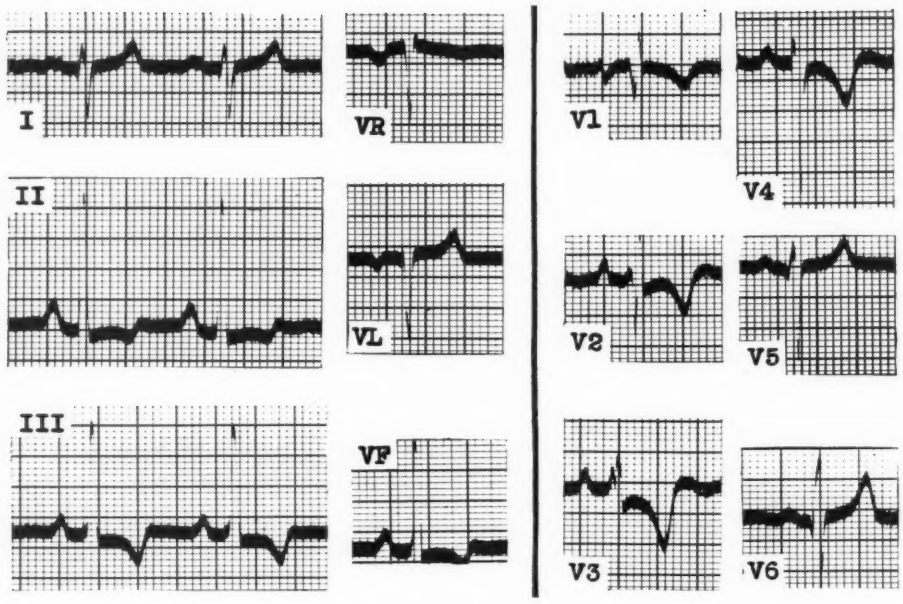

FIG. 3.—Case 3. Electrocardiogram showing right ventricular hypertrophy and incomplete right bundle branch block.

in two patients aged 3 and 6 years respectively (Cournand *et al.*, 1949; Voci *et al.*, 1951) pressure and resistance had fallen considerably some months after operation. This suggests that a sustained increase in pulmonary blood flow due to a patent ductus might cause in time an increase in pulmonary vascular resistance and a raised pulmonary arterial pressure. This is not the course of events, however, in typical cases of patent ductus arteriosus; only exceptionally has a patient with a classical continuous murmur been known to progress to severe pulmonary hypertension and loss of the murmur (Campbell and Hudson, 1952). It appears, rather, that those patients with severe pulmonary hypertension and a patent ductus arteriosus have always been atypical in that they have never been known to have a continuous murmur at an earlier stage. The relative frequency with which this combination occurs in children suggests that the pulmonary hypertension may be due to an inborn abnormality of function which resembles primary pulmonary hypertension, and is, perhaps, aggravated by the presence of the persistent ductus arteriosus.

The only conclusion that can be reached at present is that serious pulmonary hypertension is probably due to a separate abnormality, and is not merely secondary to persistence of the ductus arteriosus. There is some evidence, however, that pulmonary hypertension is made worse by the potency of the ductus, as it has on occasion been significantly relieved after closure of the ductus.

The second problem concerns the advisability of surgical closure of the ductus. In the presence of severe pulmonary hypertension operation carries an increased risk. Death has occurred at operation from tearing of a pulmonary artery (Johnson *et al.*, 1951) or in the period after the operation (Johnson *et al.*, 1950). Moreover, if the shunt through the ductus has been reversed by pulmonary hypertension, closure of the ductus will in theory increase the pulmonary arterial pressure still further. The patient reported by Swan *et al.* (1949) had a patent ductus and coarctation of the aorta, complicated by pulmonary hypertension causing reversal of the shunt. She died

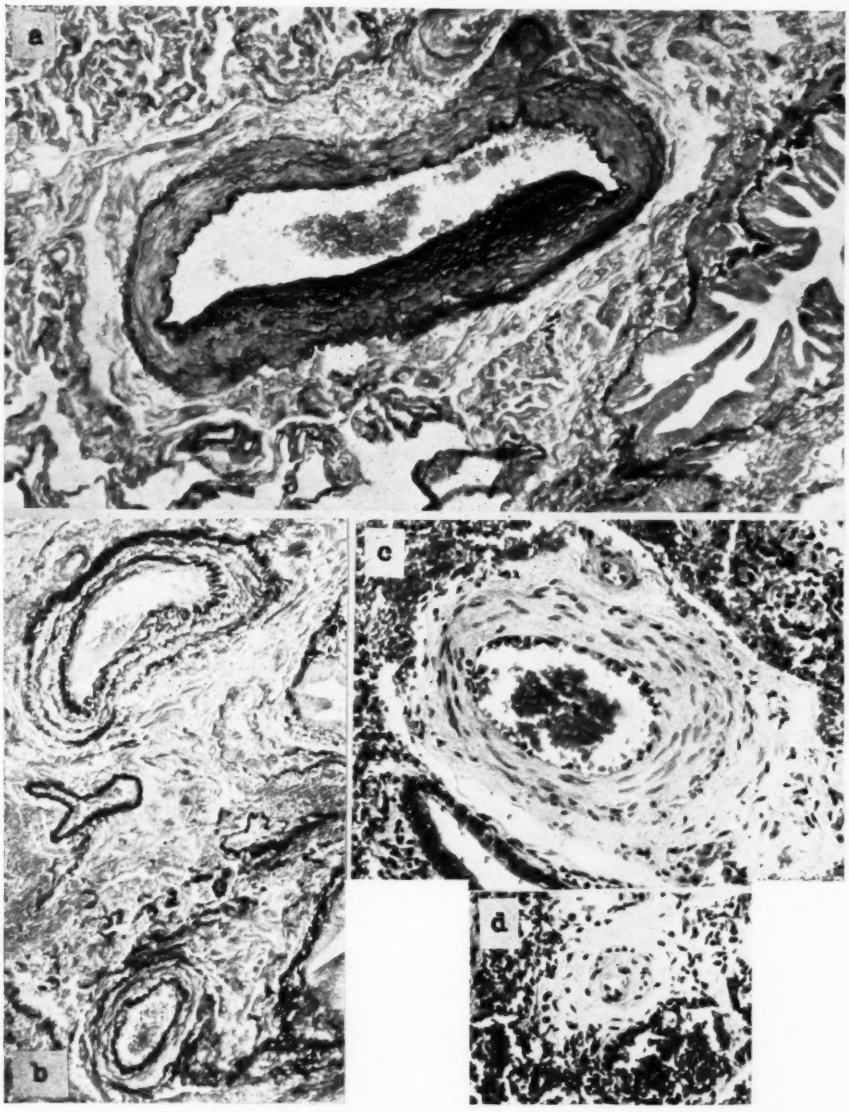

FIG. 4.—Case 3. Histology of pulmonary arteries. (a) and (b) (× 100): sections stained for elastic tissue show hypertrophy of the media and an increase in the elastic laminæ with, in (a), a raised plaque of fibro-elastic tissue in the intima. (c) and (d) (× 200) show hypertrophy of the media and arteriolosclerosis resembling that seen in systemic hypertension.

on the operating table shortly after ligation of the ductus, before resection of the coarctation could be attempted; autopsy showed an additional abnormality, an unsuspected congenital mitral stenosis. Another patient (d'Abreu, 1953), a woman of 26 with reversal of the shunt due to pulmonary hypertension, had the ductus ligated. She died on the following day with peripheral circulatory

failure and impalpable femoral pulses; there were no signs of congestive heart failure. On the other hand, successful operation and recovery have been reported in patients with pulmonary hypertension not severe enough to cause reversal of the shunt (Cournand *et al.*, 1949; Voci *et al.*, 1951; and Myers *et al.*, 1951).

It is dangerous, therefore, to ligate the ductus when pulmonary hypertension is severe enough to reverse the shunt, but while the shunt is still from the aorta into the pulmonary artery it is reasonable to ligate the ductus in the hope that pulmonary hypertension will later diminish.

The association of patent ductus with coarctation of the aorta is well known, and cases with pulmonary hypertension in addition are described by Edwards *et al.* (1949), Swan *et al.* (1949), Gotzsche *et al.* (1950), Taylor *et al.* (1950), and Johnson *et al.* (1951).

Diagnosis. The clinical recognition of the combination of patent ductus arteriosus with severe pulmonary hypertension is difficult. The symptoms are dyspnœa, possibly hæmoptysis, and cyanosis in the later stages. The signs are those of pulmonary hypertension with right ventricular hypertrophy: there is no continuous murmur, but there is a systolic murmur of variable intensity, generally maximal at the pulmonary area; the pulmonary second sound is accentuated but not widely split, and pulmonary valve incompetence may occur. The pathognomonic sign, of cyanosis greater in the lower limbs than in the upper, is only present when pulmonary hypertension is severe enough to reverse the shunt; this may occur intermittently, e.g. after effort. In the absence of this sign, confusion may occur with cases of atrial septal defect (although here there is usually right bundle branch block) and primary pulmonary hypertension. Confirmation may be sought by cardiac catheterization or angiocardiography. Even so, should the pulmonary arterial and aortic pressures be nearly equal the shunt may be so small that the diagnosis may be missed on cardiac catheterization if the catheter is not passed along the ductus into the aorta.

Summary

Three patients are described in whom patency of the ductus arteriosus was accompanied by severe pulmonary hypertension. In two the shunt through the ductus was reversed, and in the third there was coarctation of the aorta. The diagnosis was made in all by passage of a catheter along the ductus into the aorta, and confirmed in one by thoracotomy. In none was the ductus ligated. The indications for operation and the relationship between patent ductus arteriosus and pulmonary hypertension are discussed.

The three patients were under the care of Professor C. B. Perry and Mr. R. Belsey, Dr. D. H. Davies, and Dr. J. E. G. Pearson, to whom my thanks are due. I also wish to thank Dr. O. C. Lloyd for his histological report, and Miss Barbara Barter for technical assistance.

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THE ELECTROCARDIOGRAM ON THE FIRST DAY OF LIFE

BY

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Electrocardiography in the early new-born period has not been very extensively studied, although many reports have been published of cardiographic patterns in older children. With the rapid development of cardiac surgery, it is important to standardize normal cardiographic tracings to aid in the accurate diagnosis of congenital cardiac lesions as early as possible.

Nicolai and Funaro (1908) recorded the first study of electrocardiography in children. They noted the frequent presence of a deep S wave in lead 1. In 1915, Krumbhaar and Jenks commented on deep Q waves in children's cardiograms. Master *et al.* (1935) reported the first investigation of chest lead cardiography in children, and noted that in very young children the T wave frequently remained negative as far over the chest as the apex. Robinow *et al.* (1936) commented that in children 14 years of age, the T wave became similar to the normal adult. Groedel and Miller (1944) investigated electrocardiograms in the new-born infant, and observed a right heart pattern in chest leads 1 and 2, and left patterns in chest leads 5 and 6. Battro and Mendy (1946) investigated three age-groups of children, including a group 0–2 years using standard leads, unipolar extremity leads and six unipolar chest leads: in the youngest age-group, they noted a Rs pattern in V1, and frequent negative T waves up to V6. Schaffer *et al.* (1950) studied unipolar electrocardiography in the normal new born and noted the negative T waves in right-sided chest leads and upright T waves in left chest leads.

The study presented here is recorded to add to present knowledge of electrocardiography in the immediate new-born period. Tracings were taken in 15 normal new-born Bantu infants within 24 hours of birth.

Method and Results

The group of 15 normal new-born Bantu infants comprised 9 boys and 6 girls. The youngest infant was 2¾ hours old and the oldest was 21 hours (Table I). They were all submitted to a thorough clinical examination. The presence of any abnormality excluded them from this investigation. The birth weights varied from the highest level of 4 kg. to the lowest of 2·5 kg. The tracings were recorded using a Sanborn direct-writing electrocardiograph. They were taken with the infant recumbent and quiet and the following leads recorded: standard leads I, II, and III, leads aVR, aVL, aVF, V1 to V6, VS (sternal-fourth interspace level), and two right-sided chest leads in the fourth interspace. The tracings were studied from the following aspects: rate and rhythm, position, P–R interval, and general observations on the QRS, P, and T components. A typical electrocardiogram of a new-born infant is shown in Fig. 1.

The heart rate varied from the most rapid of 150 a minute in four cases, to the slowest rate of 100 a minute, in one case. The rate bore no relationship to the birth weight or the time after birth. There was normal sinus rhythm in all the tracings.

Position of the heart. All the tracings showed a negative deflection rS pattern in lead aVL and a positive deflection qR pattern in lead aVF. All these patients showed a vertical position of the heart.

P–R interval. The P–R interval varied from the longest period of 0·12 sec. in three cases, to the shortest of 0·08 sec. in four cases. In the remaining eight cases the duration of the P–R interval was 0·1 sec. There

was no relationship to the heart rate. The shortest interval of 0·08 sec. occurred both at a rate of 115 a minute and at 150 a minute.

P wave. The P wave was inverted in every tracing of lead aVR. It was inverted in one tracing of lead III and in two tracings of lead aVL. It was always upright in leads aVF and VS. Its amplitude was constantly highest in the sternal lead.

Q wave. This was present in every tracing of standard lead III and in eight cases of lead II. It was constantly present in lead aVF.

TABLE I

HEART RATE AND P–R INTERVAL IN THE FIRST 24 HOURS OF LIFE

Case	Sex	Age (hours)	Rate a minute	P–R interval in seconds
1	Female	12	115	0·10
2	Female	2¾	136	0·10
3	Female	8	115	0·12
4	Female	3¾	100	0·12
5	Female	10	115	0·10
6	Female	3½	125	0·08
7	Male	21	150	0·10
8	Male	10	115	0·08
9	Male	11	150	0·08
10	Male	20¾	150	0·08
11	Male	6½	110	0·10
12	Male	10	136	0·10
13	Male	8½	115	0·12
14	Male	18	150	0·10
15	Male	13	115	0·10

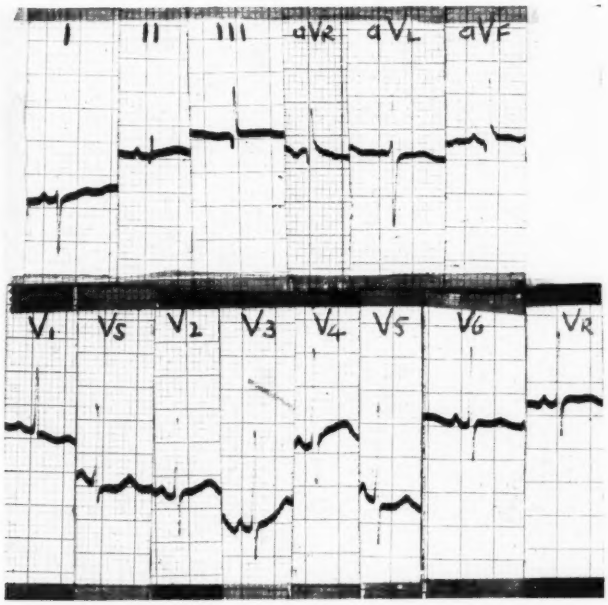

FIG. 1.—Electrocardiogram of a normal infant recorded within 24 hours of birth.

T wave. The T wave was inverted in all tracings in lead aVR. It was also inverted in three cases in lead III, and twice in lead II. In two tracings, an upright T wave became negative on passing from the right side of the chest to the left, a similar finding to that recorded by Furman and Halloran (1951). In one tracing, negative T waves on the right side of the chest became positive on passing to the left.

QRS pattern. These patterns in leads V1 to V6 varied except that the positive and negative deflections were constantly of approximately equal magnitude in leads V3 or V4. In the right-sided chest leads a large R wave was constantly present.

Discussion

In the immediate new-born period, the rhythm, position of the heart, and P–R interval appear to be fairly constant. This small series illustrates the variability of the T wave in this age-group. In two tracings the S–T segment was depressed in V2. Furman and Halloran (1951) also commented on this finding. The heart of the neonate differs from the adult in the much greater surface area of the right ventricle being in contact with the thin anterior chest wall. Richman and Master (1951) suggested the different ratio of left and right ventricular muscle mass in childhood and in the adult to explain the differing electrocardiograms. The rate varied between 100 and 150 a minute.

Summary

Electrocardiograms were taken in a series of 15 normal new-born Bantu infants within 24 hours of their birth. Nine were boys and six girls. Standard leads and the unipolar extremity and chest leads were employed. The heart was always vertical in position. The rate varied from the most rapid at 150 a minute to the slowest at 100 a minute. Normal sinus rhythm was present in all the tracings. The P–R intervals varied between 0·12 second and 0·08 second, bearing no relationship to the heart rate. Certain special features of the various components of the electrocardiogram in the new-born have been described. In two cases, an upright T wave became negative on passing from the right side of the chest to the left, and once a negative T wave on the right side became positive on passing to the left. The QRS patterns in the chest leads varied, transition occurring between V3 and V4. A large R wave was always present in the right-sided chest leads.

I wish to thank Dr. Seymour Heymann, Head of the Department of Pædiatrics, University of the Witwatersrand, for his advice and criticism. I must also thank Dr. Eric Kahn for facilities offered and the Obstetrics Department, Baragwanath Hospital, for providing the patients for study.

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THE LEFT AURICULAR APPENDAGE IN MITRAL STENOSIS

BY

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Since the introduction of the operation of mitral valvotomy much interest has been aroused in the histological changes found in biopsy specimens of the left auricular appendage. Some workers have recorded a high incidence of lesions resembling Aschoff nodules, and since these are found in patients in whom no rheumatic activity is apparent clinically, there has been much speculation as to their precise nature and significance. A review of the histological studies of rheumatic heart disease gives no indication of the frequency with which the appendage is involved in active carditis, nor of the morphology of the specific lesions in this site, since the appendage is not usually examined histologically. It is the purpose of this investigation, therefore, not only to record the findings in biopsy specimens of the left auricular appendage from patients who have had valvotomy, but also to study the appendage in patients who have died with mitral stenosis, in order to assess the full significance of the various lesions observed in this structure in patients suffering from chronic rheumatic heart disease.

Auricular Appendages from Valvotomy Cases

Fifty-three appendages from patients who had mitral valvotomy were submitted for histological study, and in 24 lesions that were interpreted as Aschoff nodules were found. The nodules were observed within the endocardium or in the subendocardial zone, and in two cases in the myocardium of the appendage as well. The frequency of lesions in each appendage varied considerably, as also did their structure. In their most characteristic form they consisted of collections of large mononuclear and multinucleated cells, with abundant slightly basophilic cytoplasm. They were arranged in coronal or mosaic fashion in the vicinity of collagen fibre that had undergone fibrinoid change; a mantle of lymphocytes frequently surrounded the nodule, and the overlying endocardium showed much œdema (Fig. 1 and 2). Occasionally the Aschoff cells formed palisades within the endocardium between swollen collagen fibres, reproducing the banded appearance of rheumatic endocardial lesions described by McCallum (1924) and Gross (1935).

In some instances "doubtful" Aschoff bodies were noted; for example, nodules without fibrinoid change in the ground substance, and others in which the Aschoff cells, though maintaining a coronal arrangement, appeared shrunken and fibroblastic in character. Still others assumed the structure of a rather cellular spindle-shaped scar. Similar appearances have been described by other workers and have been referred to as "possible" or "probable" rheumatic lesions, or have been emphatically discounted as evidence of active rheumatism. Attention has been drawn by Gross and Ehrlich (1934) and McKeown (1945) to the cyclical changes that occur in the Aschoff nodule in the myocardium of the left ventricle. There, the nodule evolves initially from a focus of damaged collagen, about which the Aschoff cells become concentated; as healing takes place the change in the ground substance disappears, the Aschoff cells assume a spindle-shaped form, and finally a fibrillar scar results: this cycle may take 6–9 months to complete. Such changes have also been attributed to nodules in the endocardium of the left auricle by Gross and Ehrlich (1934) but are believed to be somewhat modified by the density of the tissue in which they occur. An attempt was therefore made in the present study to identify, if possible, the different phases of evolution of

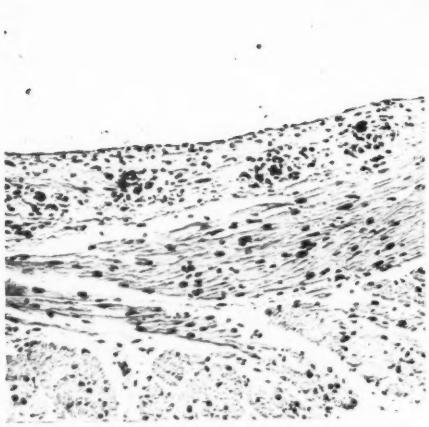

FIG. 1.—Low-power view of the appendage showing several Aschoff nodules in the endocardium (× 64).

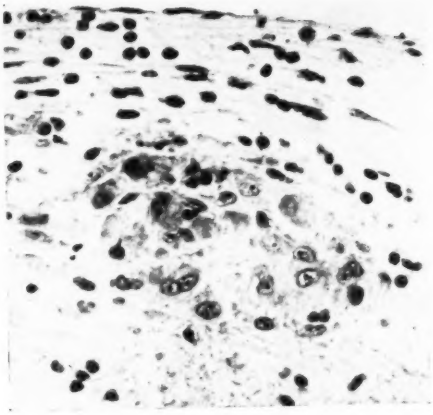

FIG. 2.—Endocardial Aschoff nodule, composed of large monc- and multi-nucleated cells arranged in coronal fashion around a focus of altered collagen (× 360).

the endocardial nodule, and to reconstruct in some measure, a life cycle comparable to that of the myocardial Aschoff nodule. The early exudative phase was recognized by the presence of marked fibrinoid degeneration in the ground substance and a sparse cellular reaction (Fig. 3), the fully developed nodule consisted of mature Aschoff cells with a coronal or mosaic arrangement (Fig. 4). The healing lesion showed elongation of the Aschoff cells (Fig. 5) and later the formation of a cellular spindle-shaped scar (Fig. 6). The stage of complete healing could not be recognized with certainty. These phases were best seen in the subendocardial zone where the connective tissue is loose and fibrillar. In the endocardium proper, where the ground substance is much more dense, the Aschoff nodules appeared to have a less distinctive life cycle. Acute lesions could be readily identified and had a fully characteristic structure, but regressing lesions often seemed to consist of

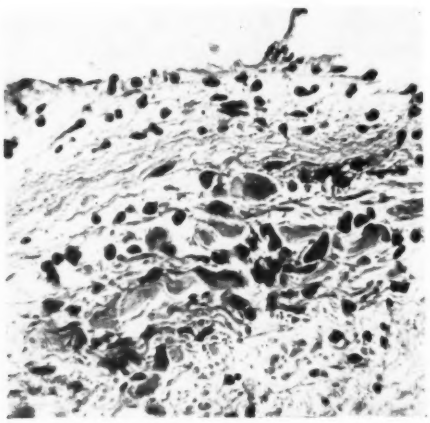

FIG. 3.—Aschoff nodule in early stage of development, showing marked fibrinoid change in ground substance and commencing cellular reaction (× 360).

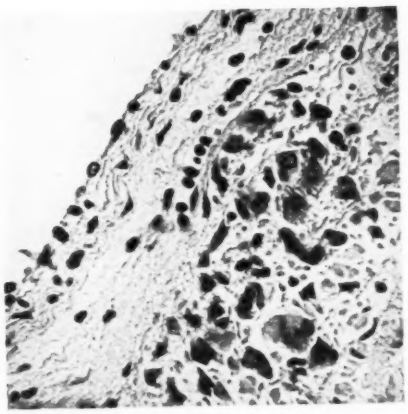

FIG. 4.—Fully developed nodule, with numerous large Aschoff cells in subendocardial zone (×360).

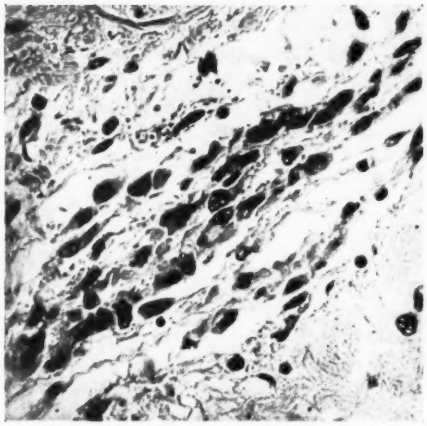

FIG. 5.—Polarizing nodule showing elongation of Aschoff cells (× 360).

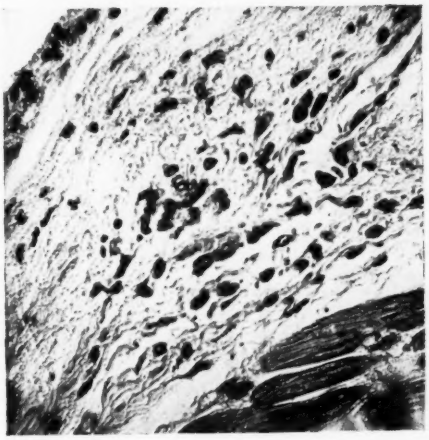

FIG. 6.—Aschoff nodule in later stage of healing, showing fibroblastic character or cells and formation of scar tissue (× 360).

radially arranged collections of darkly staining spindle-shaped cells, and had few of the distinctive features of healing lesions in other sites. The presence of such "doubtful" lesions has been stressed by many workers and has been one of the main reasons for disputing the specificity of the biopsy findings, but from the evidence available it is at least strongly suggestive that they represent nodules in which the phases of healing are less characteristic because of their situation in dense fibrous tissue.

As further evidence against the specificity of the biopsy lesions Enticknap (1953) has pointed out that the distribution of the nodules is unusual for rheumatic carditis in that they are almost invariably confined to the endocardium. Yet in 20 cases of acute rheumatism studied in this department only one had Aschoff nodules in the myocardium of the auricle, and in Gross' series (1935) of patients who had had repeated attacks of rheumatism and had histological evidence of activity post mortem only 1 in 28 had Aschoff nodules in the auricular myocardium. Thus the relative absence of myocardial nodules in the appendage of valvotomy cases is to be expected, if rheumatic lesions in this site are in any way comparable to those occurring in the wall of the left auricle. On histological grounds, therefore, the structure, evolution, and distribution of the lesions in biopsy specimens is essentially that of the specific Aschoff nodule of active rheumatic carditis.

The main reason for doubting the specificity of the biopsy findings is the complete lack of clinical signs of rheumatic activity in patients with positive lesions. It is generally accepted, however, that the absence of manifest symptoms does not preclude the existence of acute rheumatism. Many patients with mitral stenosis give no antecedent history of rheumatic fever. Some have suffered from one clinical attack only, and it is unlikely that this alone is responsible for the degree of valvular damage that ultimately develops. Repeated subclinical attacks of the type observed in biopsy specimens are much more likely to be responsible for the progression of the valvular lesion. There are many references to cases of mitral stenosis with unexpected evidence of rheumatic activity at autopsy, e.g. Rothschild *et al.* (1934), Gross (1935), Rogers and Robbins (1947), McKeown (1948), (1950), Graham *et al.* (1951), Pinniger (1951), and Waaler (1952). All such observations, in conjunction with the results of biopsy studies, stress the frequency of subclinical attacks of rheumatism, and emphasize the need for new clinical tests for assessing rheumatic activity.

The high incidence of Aschoff nodules in this biopsy series is in accord with the experience of other workers. Pinniger (1951) found nodules in 10 of 15 amputated appendages, Janton *et al.* (1952)

in 14 of 88, Sabiston and Follis (1952) in 32 of 43, Waaler (1952) in 3 of 12, Kuschner *et al.* (1952) in 4 of 11, Biörck *et al.* (1952) in 6 of 18, Wylie (1952) in 4 of 9, and Enticknap (1953) in 29 of 71 cases. In Sabiston's series there appeared to be some correlation with the sedimentation rate as no patient having a raised sedimentation rate failed to show lesions. In the present series, however, only one patient with active endocarditis had a slightly raised rate (16 mm./1 hr.) and much higher readings were encountered in patients without carditis. Neither was there any relationship between the age of the patient and the occurrence of rheumatic activity.

It is not yet fully established whether these lesions in the appendage denote a widespread rheumatic carditis, but it is essential that this aspect of the problem should be investigated, for it may have an important bearing on the immediate and long-term prognosis. Four patients in Biörck's series (1952) died following operation and the autopsies in these cases were all completely in agreement with the biopsy picture, with no rheumatic activity detectable in any part of the heart. Ellis *et al.* (1951) found no other evidence of activity post mortem in two patients in whom biopsy specimens of the appendage taken a few hours before death showed Aschoff nodules. On the other hand, Pinniger (1951) confirmed the presence of active rheumatism in the myocardium of the left ventricle in one patient who had positive biopsy findings. Information of this nature should prove of value in assessing the significance of the biopsy lesions but will inevitably take time to accumulate since in any given valvotomy series the immediate mortality is low. For this reason a study of the appendage in post-mortem cases of mitral stenosis was undertaken, with the purpose of investigating the incidence of, and relationship between, active rheumatic lesions in this site and in other regions of the heart.

The Auricular Appendage from cases of Mitral Stenosis (Post Mortem)

Sections of the left auricular appendage were available for study in 92 cases of mitral stenosis on the post-mortem files of this department. The appendage was taken for examination either because it contained a thrombus, or because there was evidence of systemic embolization. More recently it has been taken routinely in all cases of mitral stenosis. There was a history of previous rheumatic fever in 45 patients. Clinically all were considered quiescent. Congestive heart failure was present during their terminal illness in 67 patients, 11 died directly from the effects of embolism, and the remainder from causes unrelated to their cardiac condition.

The left auricular appendage and a block that included the wall of the left ventricle, mitral valve, and left auricle were studied in each case, and the frequency of Aschoff nodules noted in these sites. In 70 hearts no rheumatic activity was detected in either the appendage or routine section. In 17 hearts Aschoff nodules were present in both sites, and in 5, nodules were noted in the myocardium of the left ventricle only (Table I.)

TABLE I

Aschoff Nodes in Patients Dying with Mitral Stenosis

Mitral stenosis No. of cases (92)	Aschoff nodes in L. A. appendage	Aschoff nodes in left ventricle
70	−	−
17	+	+
5	−	+

In this somewhat selected series of clinically quiescent cases of mitral stenosis the total incidence of active rheumatic lesions is 24 per cent, and corresponds closely with the observations of Gross (1935) who recorded an incidence of 25 per cent in similar cases, and Pinniger (1951) who found 31 per cent of cases of mitral stenosis with definite Aschoff nodules. These findings lay further emphasis on the frequency of subclinical rheumatism. In an analysis of the positive cases the

results tend to support the contention that Aschoff nodules in the left auricular appendage denote a generalized rheumatic carditis, since in 17 cases in which nodules were present in the appendage they were accompanied by similar lesions in the left ventricular myocardium. Their absence from the appendage in 5 cases in which they were noted in the wall of the left ventricle is in accord with the known distribution of rheumatic lesions in the heart, the routine section being taken close to the mitral posterior block which Gross *et al.* (1930) have demonstrated to be one of the sites of election of the rheumatic process. The highest incidence of lesions is found in this block and in a block of the tricuspid valve and septum. It might be added that in these 5 cases, only occasional nodules were seen and they were usually in the stage of polarization. In the cases in which active rheumatic lesions were found in both appendage and left ventricle the structure of the lesions in each site was similar, the same phase or phases of activity being represented. It was also observed that the frequency of nodules in the appendage and in the myocardium of the left ventricle in each case corresponded closely, and in only one was the involvement heavy (Fig. 7 and 8).

FIG. 7.—Appendage from post-mortem case of mitral stenosis, showing heavy involvement of endocardium by Aschoff nodules with a "banded" appearance (× 145).

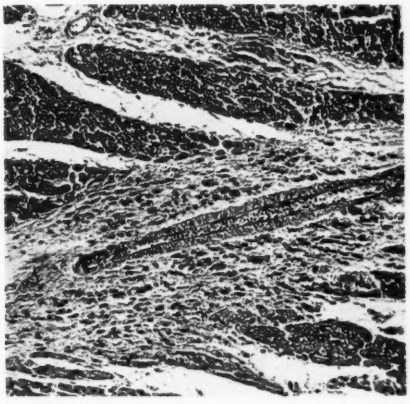

FIG. 8.—Myocardium of left ventricle, same case, showing multiple nodules in septa (× 80).

CONCLUSIONS

This combined study of biopsy and post-mortem sections of the left auricular appendage reveals a relatively high incidence of acute rheumatic lesions in this structure, in the complete absence of clinical signs of rheumatic activity. It is evident from analysis of post-mortem cases of mitral stenosis that a close correlation exists between the incidence and frequency of Aschoff nodules in the appendage and in the left ventricular myocardium. It would seem that the changes noted in the appendage reflect closely the state of the rest of the heart as far as rheumatic activity is concerned, except that occasionally the appendage may be spared when the rest of the heart is involved. That such a relationship exists should be of value in the interpretation of the significance of biopsy findings.

It is difficult to explain the absence of complications after operation in patients with histological evidence of active endocarditis. In some the rheumatic episode may be regressing, in others the relatively slight involvement of the appendage suggests a mild attack. Yet it is felt that active carditis in valvotomy patients may constitute a hazard and may precipitate or contribute in some measure to a fatal outcome. It is even possible that in the period before operation it may be one

of the factors responsible for the aggravation of symptoms that renders operative treatment necessary.

It is to be hoped that the full significance of these subclinical episodes of rheumatic activity will ultimately be assessed by a prolonged clinical and pathological follow-up of all patients having a mitral valvotomy.

Summary

The histological findings in 53 biopsy specimens of the left auricular appendage are recorded. In 24, lesions were observed that showed the same distribution, structure, and evolution as the specific Aschoff nodule. A study of the appendage in 92 post-mortem cases of mitral stenosis is also presented, 17 cases showing Aschoff nodules in the appendage and in other parts of the heart. It is concluded that rheumatic nodules in the appendage denote a generalized rheumatic carditis, and the extent to which the appendage is affected reflects closely the degree of involvement of the left ventricle. The significance of these observations in relation to biopsy findings is discussed.

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THE USE OF THE PURE VERATRUM ALKALOIDS NEOGERMITRINE AND PROTOVERATRINE IN HYPERTENSION

BY

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The veratrum alkaloids were used clinically prior to the detailed knowledge of their pharmacology, Baker (1860) describing the successful treatment of a case of eclampsia. The pharmacological actions of the alkaloids were reported by Prevost in 1866, and von Bezold and Hirt (1867) attributed the fall in blood pressure and bradycardia to vagal reflexes arising from the heart itself. Cramer (1915) thought these actions were due to a vagal reflex from the lungs.

The pure alkaloid protoveratrine, derived from *veratrum album*, was studied by Krayer *et al.* (1944, 1946), renewing clinical interest in the veratrum alkaloids. They reported that the hypotensive effect was due to the presence of ester alkaloids like protoveratrine. They confirmed the work of von Bezold, reporting that the afferent impulses producing the reflex fall in blood pressure arose mainly in the heart, and agreed with Cramer that some afferent impulses were derived from the lungs and suggested that the "carotid sinus area" was concerned, the latter suggestion being supported by the observations of Aviado *et al.* (1949).

Freis *et al.* (1949), in an investigation of the hæmodynamic effects of the veratrum alkaloids (vertavis and veratrone) in man, reported that the hypotensive effect was due to a decrease in peripheral resistance in the limbs and splanchnic areas without any fall in cardiac output. The decrease in peripheral resistance was apparently caused through the sympathetic nervous system as the drugs did not increase the peripheral blood flow in sympathectomized limbs, whereas they did so in normally innervated limbs. They found that the alkaloids were not sympatholytic, for pressor reflexes were maintained and postural hypotension did not occur.

Authors using various preparations of mixed veratrum alkaloids in the treatment of hypertension are in agreement that in some patients toxic reactions prevent the administration of effective hypotensive doses. Some authors (Hite, 1946; Freis and Stanton, 1948; Faust, 1951) found these patients to be in a minority, while others (Coe *et al.*, 1950; McNair *et al.*, 1950; Kauntze and Trounce, 1951; Barrow and Sikes, 1951: Smirk and Chapman, 1952) thought they were in a majority. There is general recognition, however, that these alkaloids, were it not for the frequency with which toxic side effects occur, would be suitable therapeutic agents in the treatment of hypertension, since they do not impair sympathetic reflexes or cause marked postural hypertension except in toxic doses. Furthermore, they are effective by mouth, and the effect of a single dose is maintained for several hours; the wide variations in arterial levels that may be produced by ganglion blocking agents such as the methonium compounds are thus avoided.

Some clinical observations have been made also with pure veratrum alkaloids. Meilman and Krayer (1950), in a study of the action of protoveratrine given intravenously in man, found that a significant fall of blood pressure could be produced without serious complications.

In 1950, Freis *et al.* reported the use of two previously undescribed crystalline alkaloids of *veratrum viride*, germitrine and germidine, both of which exhibited strong hypotensive activity in

man when given orally or intravenously. They concluded that the toxic effects of extracts of *veratrum viride* were not derived entirely from contaminating constituents in the drug, since similar reactions followed administration of the pure crystalline alkaloids.

Our objects are (1) to examine the effects of oral veratrum therapy in hypertensive patients, using the pure alkaloids neogermitrine and protoveratrine, and various alkaloidal mixtures such as anatensol, vertavis, and a mixed alkaloid preparation from Messrs. S. B. Pennick & Company, and (2) to compare the effects of neogermitrine and protoveratrine given by mouth and by injection, with particular reference to toxic manifestations. The observations have been made on 65 patients suffering from hypertension of varying ætiology, mostly essential hypertension.

Materials and Methods

Using the general method described by Fried *et al.* (1949, 1950), a supply of the pure alkaloids of *veratrum viride* was prepared by Mr. W. G. H. Edwards of the Chemistry Department, University of Otago, to whom we are indebted for the following summary of the method of extraction.

A total of 40 lb. of the dried roots was extracted in two batches with benzene (33 gallons) and 0·880 ammonia ($1\frac{1}{2}$ litres) until the concentration of solid in the extract fell to 0·1 g./litre. Evaporation *in vacuo* was effected in a 10-gallon still and was carried to a volume of $2\frac{1}{2}$ litres.

The further extraction of this was carried out according to the paper quoted above, giving the following fractions :

(*a*) a jervine–veratramine fraction (about 50 g.),
(*b*) a rubijervine–isorubijervine fraction (7·0 g.),
(*c*) secondary bases—isolated as acetyl derivatives, and
(*d*) 3–4 g. of biologically active material, which on assay in the hypertensive patient was active in doses of 1–2 mg.

Fraction (*d*) was submitted to 24 cell Craig distribution between benzene and 2-molar acetate buffer of *p*H 5·5. This distribution did not parallel that of the American workers, since only one more fraction appeared to be obtained, together with two smaller fractions and two intermediate ones. These are related as below.

Fraction I	0·6 g.	Cells 2–8 inclusive
Fraction II	1·6 g.	Cells 9–14 inclusive
Fraction III	2·25 g.	Cells 15–17 inclusive (Intermediate fraction)
Fraction IV	0·45 g.	Cells 18–21 inclusive
Fraction V	0·17 g.	Cells 22–23 inclusive (Intermediate fraction)

Fraction II was found in biological assay to have about five times the activity of germidine, and chemical studies of this fraction by Mr. Edwards of the Otago University and by Dr. Wintersteiner of the Squibb Institute for Medical Research showed it to be neogermitrine.

Selection of Cases

The patients in whom the trials were made had been referred to the clinic because of high casual blood pressure readings and in the majority of them symptoms of hypertension were present. In most patients the basal blood pressures (Smirk, 1944; Kilpatrick, 1948) were also considerably raised. Patients who exhibited labile hypertension, with high casual blood pressures but much lower basal blood pressures, were not excluded from the trials, as many had had hypertensive symptoms for some time, and most had supporting radiological or electrocardiographic evidence of left ventricular hypertrophy. In some patients with low basal blood pressures who apparently responded well to veratrum therapy, a trial with an inert substance was made.

Blood pressures were recorded in accordance with recommendations of the Committee for the Standardization of Blood Pressure Readings of the American Heart Association and of the Cardiac Society of Great Britain and Ireland (1939).

The case numbers used correspond with those in earlier publications (Smirk and Alstad, 1951; Smirk and Chapman, 1952).

Intravenous Administration. The patients were lying in a quiet room. Several estimations of the blood pressure were made over a preliminary period of about 10 minutes. Tuberculin syringes were mounted in a micrometer device (Fig. 1), such that one complete turn of a screw delivered 0·2 ml. (0·04 mg.) of a solution of 0·02 per cent neogermitrine in 0·1 per cent acetic acid. The syringe was connected to the intravenous needle by a length of rubber pressure tubing with a

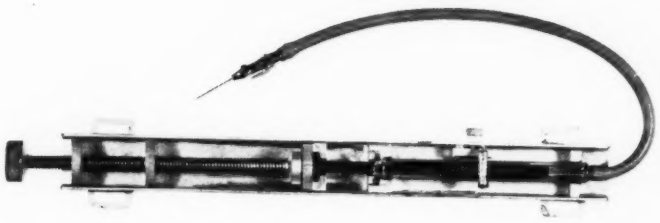

FIG. 1.—Micrometer syringe emptying device.

capillary bore. Small intravenous injections of neogermitrine were administered at two-minute intervals with estimation of the blood pressure and pulse rate. When the blood pressure had fallen to near normal or to hypotensive levels, or if toxic symptoms appeared, the needle was withdrawn. Blood pressures and pulse rates were then measured in the recumbent and erect postures until the readings had reached their previous level.

Oral Trials. After preliminary recordings of the blood pressure and pulse rates the veratrum preparation to be tested was given—usually fasting, but on occasion after food. Blood pressure and pulse rates were recorded with the patient in the sitting and erect postures at half-hourly intervals, and the onset and duration of any toxic manifestations were recorded.

Where a good fall of blood pressure could be obtained without appreciable toxic effect the patient was subsequently treated as an out-patient with either a mixed or a pure alkaloidal preparation. Symptomatic relief without effective blood pressure control has not been the aim of the present investigation.

RESULTS

Administration of Inert Control Substances. Eleven patients received either diluted Tr. capsicum by mouth or an injection of sterile normal saline solution. The patients were unaware of the substitution, and the blood pressures were recorded in the usual manner. In eight patients, falls in the systolic level of more than 30 mm. Hg occurred after the administration of one or other of these substances. A typical example was Case 268, in whom the resting minimum blood pressure was 198/128, readings of 168/110 being noted 1½ hours after the injection of 1 ml. of normal saline. Hence, we have disregarded falls in blood pressure of under 40/20 mm. Hg as being possibly due to spontaneous variation. A fall in blood pressure of this order was obtained in many patients taking veratrum alkaloids without significant toxic effects, but we feel that many of these falls in blood pressure are due to a placebo action and are not related to the specific effect of the drug administered. It may be assumed in the clinical trials that follow that only blood pressure falls which exceed 40/20 are regarded as likely to be due to the specific action of the veratrum alkaloids.

Parenteral Administration of Pure Veratrum Alkaloids. (*A*) *Intravenous Neogermitrine.* Twenty-one patients were given neogermitrine intravenously. The initial dose was usually 0·04 mg. Injections of 0·02 mg. at two-minute intervals were then given until the blood pressure began to fall. The dose was then further reduced to 0·01 or 0·005 mg. at two-minute intervals until the blood pressure had reached a systolic level of about 120 to 130 mm. Hg, or until toxic manifestations had

occurred. The needle was then withdrawn. The total dose given ranged from 0·09 mg. to 0·42 mg., and the time taken for these doses to be administered was 8 to 30 minutes. The blood pressure and the pulse rate usually fell by stages as more drug was given (Fig. 2), but in some patients no effect was observed until a critical level was reached, very small doses then producing a large fall. The precipitous fall of blood pressure occurring when a critical dose is attained and after the

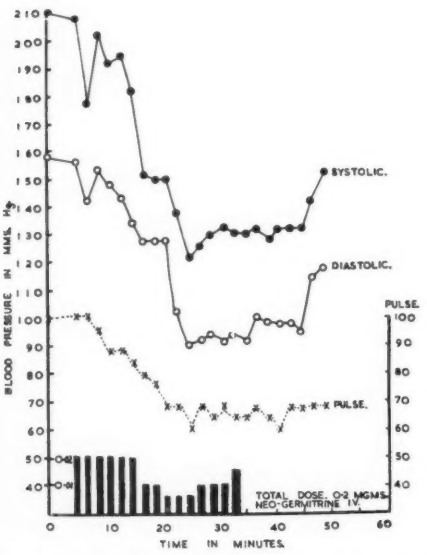

FIG. 2.—Example of slowly progressive fall of blood pressure and pulse rate as the dose of neogermitrine is gradually increased.

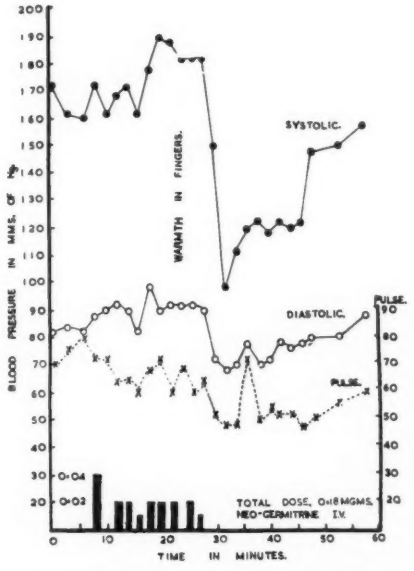

FIG. 3.—Example of abrupt fall of blood pressure beginning at a critical dose in the course of slow injection of neogermitrine.

addition of only 0·005 mg. (Fig. 3) shows how important it is to approach effective dosage circumspectly from below.

In 17 out of the 21 patients the minimal blood pressure levels in the recumbent position after neogermitrine lay between 132/80 and 90/60, the average blood pressure fall during the test being 116/58. In the remaining 4 patients the injection had to be stopped because of the onset of toxic or premonitory toxic manifestations and consequently the blood pressures did not fall so low, the minimum levels lying between 192/100 and 152/108, the average fall being 85/50. The pulse rate usually fell to below 60.

In all, toxic or premonitory toxic manifestations (for detail see later) occurred in 6 patients and were transient, discomfort lasting for about 10 minutes. By contrast, the fall in blood pressure might last one hour or more (Fig. 4). On occasion the blood pressure continued to fall after injection ceased. A considerable additional fall in blood pressure occurred in the erect posture without the development of toxic effects (Fig. 4).

(*B*) *Subcutaneous Neogermitrine.* As trial doses of intravenous neogermitrine induce effective falls in blood pressure with but little toxic effect, it was decided to explore the therapeutic possibilities of subcutaneous injections. Intramuscular and subcutaneous injections of veratrum alkaloids are most painful unless a local anæsthetic is added. A preparation of 0·05 per cent neogermitrine and 1 per cent procaine may be given subcutaneously, though local pain is not always avoided.

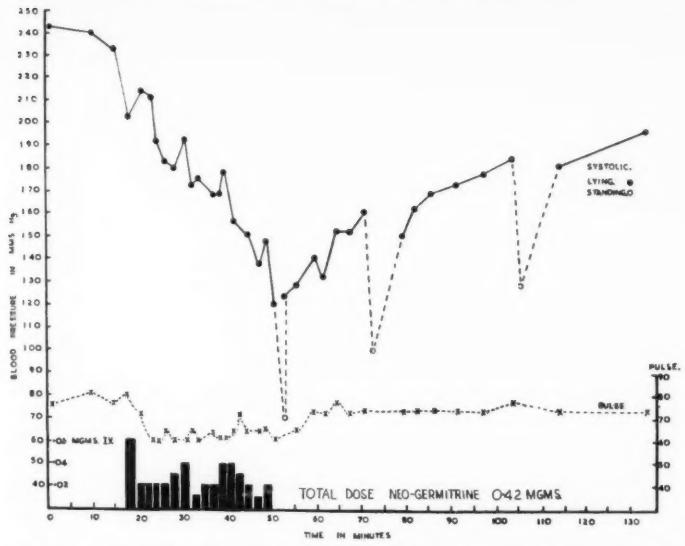

FIG. 4.—Prolonged blood pressure fall persisting after intravenous neogermitrine, with demonstration of postural hypotension.

Seven patients who had been unable to tolerate veratrum given by mouth were treated by subcutaneous injections of neogermitrine. Doses which led to an effective fall in blood pressure caused vomiting in 2 out of 7 patients. The 5 patients who appeared to tolerate effective doses of neogermitrine given subcutaneously, were given a period of trial therapy using this route of administration. The results were disappointing, as 3 out of the 5 developed toxic symptoms and treatment could not be continued. It is concluded that the subcutaneous injection of neogermitrine is not likely to provide effective treatment over long periods in many of the patients whose blood pressure levels cannot be controlled by oral administration.

(*C*) *Intravenous Protoveratrine.* Six patients were given protoveratrine intravenously, either in a single dose or fractionally administered as with neogermitrine. The effective intravenous dose was from 0·19 mg. to 0·30 mg.

The blood pressure falls more slowly after protoveratrine than after neogermitrine. The onset of the fall is ordinarily 10 minutes after injection and the maximum fall 15 minutes after. As with neogermitrine, effective doses usually cause bradycardia. The *fall* in blood pressure was 60/34, 106/72, 108/74, 154/74, 100/62, 120/70, from levels of 214/128, 204/138, 186/128, 232/132, 198/126, 230/130 respectively. Nausea occurred in one test.

(*D*) *Subcutaneous Protoveratrine.* Five of the patients who had already received neogermitrine were given subcutaneous injections of protoveratrine (with 1 per cent procaine). The results were similar to those obtained by subcutaneous injection of neogermitrine, toxic effects appearing in the same patients. It is clear that in acute experiments protoveratrine is better tolerated parenterally than by oral administration in the sense that there are larger blood pressure falls with less general toxicity.

It has not yet been decided whether continued subcutaneous injections of protoveratrine are feasible in a large proportion of patients, but the impression was gained that the margin between therapeutic and toxic effects narrowed with continued administration.

TABLE I

EFFECTS ON BLOOD PRESSURE AND PULSE RATE OF NEOGERMITRINE ADMINISTERED INTRAVENOUSLY

Case No.	Before administration		Dose	After administration		Blood pressure fall	Duration of blood pressure fall (min.)	Toxic effects
	Blood pressure (mm. Hg)	Pulse rate		Blood pressure (mm. Hg)	Pulse rate			
98	194/142	84	0·125 mg.(15)	100/82	48	94/60	30	Nil
169	210/158	100	0·11 mg.(10)	122/90	60	88/68	40	Nil
207	244/170	80	0·17 mg. (15)	152/98	48	92/72	60	Vomiting
203	242/164	96	0·195 mg. (20)	90/60	64	152/104	45	Nil
167	220/164	88	0·15 mg. (24)	116/76	44	104/88	60	Nil
165	188/112	94	0·16 mg. (18)	102/62	40	86/50	60	Nausea Hiccough
137	284/144	88	0·165 mg. (22)	116/78	40	168/66	60	Nausea
40	230/140	88	0·09 mg. (14)	92/70	60	138/70	10	Nil
263	210/130	88	0·11 mg. (8)	100/76	52	110/54	25	Nil
77	190/98	80	0·20 mg. (22)	98/68	48	92/30	70	Nil
171	240/138	88	0·12 mg. (10)	104/80	40	136/58	30	Nil
82	200/110	92	0·17 mg. (27)	104/70	64	96/40	80	Nil
152	238/122	88	0·15 mg. (15)	132/80	50	106/42	25	Nil
110	300+/178	108	0·15 mg. (20)	192/100	62	108/78	10	Nausea
183	208/108	76	0·145 mg. (22)	112/70	50	96/38	80	Nil
268	248/102	96	0·21 mg. (20)	122/68	70	126/34	35	Nil
162	242/110	80	0·42 mg. (30)	120/82	60	122/28	60	Nil
258	256/122	86	0·32 mg. (33)	176/92	60	80/30	10	Salivation
204	244/170	80	0·27 mg. (22)	182/108	56	62/62	5	Vomiting
100	248/148	84	0·17 mg. (13)	102/78	48	146/70	50	Nil
1Y	200/108	84	0·17 mg. (14)	98/60	44	102/48	90	Nausea

Figs. in brackets mean minutes.

ORAL ADMINISTRATION OF PURE VERATRUM ALKALOIDS

The response of 39 patients to oral neogermitrine or protoveratrine were studied and compared with their responses to various mixed veratrum alkaloid preparations. Twelve patients received trials both with neogermitrine and with protoveratrine, an additional 22 had neogermitrine alone, and an additional 5 protoveratrine alone.

(*A*) *Neogermitrine.* Thirty-four patients had trials with oral neogermitrine. The lowest oral dose of neogermitrine that produced a useful fall of blood pressure was 0·4 mg., and the largest single dose given was 1·4 mg. The usual single effective dose was between 0·5 mg. and 0·8 mg.

In most patients doses of 0·1 mg. below the optimum dose caused no significant fall of blood pressure, and doses of 0·1 mg. too great led to marked toxic symptoms and profound hypotension. In 16 out of the 34 patients there was no difference between the toxic and effective doses, and toxic manifestations preceded or coincided with significant hypotensive effects. In 8 out of the 34 patients the margin between doses producing significant falls in blood pressure and doses producing toxicity was less than 0·1 mg., and in this group of patients the effect of oral administration was not constant enough to allow such a small difference to be of therapeutic value. Attempts to use divided dosage in these patients were not successful (Fig. 5).

In the remaining 10 patients, however, the difference between the therapeutic and the toxic dose was more than 0·1 mg., and in these patients reduction of blood pressure could be achieved in acute experiments without significant toxic manifestations. The doses of neogermitrine used on patients treated successfully were similar to those producing toxic effects in other patients, so that freedom from toxic effects was not always related to the size of the dose.

(*B*) *Protoveratrine.* Seventeen patients were given protoveratrine by mouth. The doses of protoveratrine used ranged between 0·5 mg. and 2·0 mg. the usual effective dose being between 1·0 and 1·25 mg. Dosage was as critical for each patient as with neogermitrine.

In 5 out of the 17 patients the same dose caused hypotensive effects and toxic effects; in 6 of the 17 patients a small difference of 0·25 mg. occurred, while in the remaining 6 patients the thera-

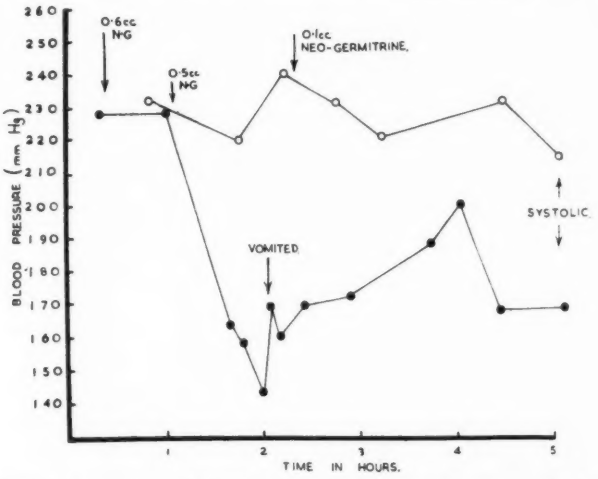

FIG. 5.—Attempt to avoid toxic effects from 0·6 mg. of neogermitrine by giving 0·5 mg. followed by 0·1 mg. one hour later led to diminution of hypotensive action.

peutic and toxic doses differed by more than 0·25 mg. As with neogermitrine, the size of dose in successful and unsuccessful patients was similar.

Postural falls of blood pressure was not severe after oral administration except following toxic symptoms. In patients taking the drugs regularly little difference in blood pressure in varying postures was observed.

COMPARISON OF EFFECTS OF PURE AND MIXED ALKALOIDS

Most of the 39 patients who have received trial doses of the two pure alkaloids have also been given trial doses of various mixed alkaloidal preparations. In addition, we have compared the results of the trials with mixed alkaloids that were reported by Smirk and Chapman (1952) with the effects of the pure alkaloids in this series.

There appears to be no important difference between the effects of neogermitrine or protoveratrine and the mixed alkaloid preparations when administered orally. Neogermitrine appears to be the most powerful preparation, being about $1\frac{1}{4}$ times as effective as protoveratrine. The mixed alkaloids are considerably less active, exhibiting about one-fifth to one-tenth the activity of neogermitrine on oral administration.

The pure alkaloids act more rapidly, having their maximum effect in from 1 to $1\frac{1}{2}$ hours, as compared with the 2—3 hours for the mixed alkaloids. Thus in Case 152 the maximum blood pressure fall both with neogermitrine and protoveratrine was at $1\frac{1}{4}$ hours, while the mixed alkaloids had their maximum action $2\frac{1}{2}$ hours after administration.

Toxic effects of neogermitrine and protoveratrine did not differ significantly from those of veratensol, vertavis, or the amorphous mixed alkaloids. They consist of such symptoms as a burning sensation in the mouth, followed by a retrosternal choking sensation, hiccough, salivation,

TABLE II

EFFECT ON BLOOD PRESSURE OF ORAL ADMINISTRATION OF NEOGERMITRINE

Case No.	Maximal subtoxic dose (neogermitrine) (mg.)	Blood pressure fall	Toxic dose (mg.)	Blood pressure fall	Result of test
191	0·85	10/6	0·9	73/34	Failed
61	0·5	32/12	0·55	48/16	Failed
258	0·7	52/44	0·8	74/32	Success
203	0·75	90/20	0·75	100/46	Failed
162	1·0	84/46	1·1	130/56	Success
202	0·55	56/32	Not reached	—	Success
161	0·55	0/0	0·6	20/5	Failed
103	0·7	40/28	0·8	82/68	Failed
268	0·6	42/16	0·65	84/66	Failed
221	0·4	21/12	0·5	44/32	Failed
40	0·5	16/6	0·6	78/44	Failed
171	0·6	18/6	0·7	84/36	Failed
165	0·8	74/32	Not reached	—	Success
137	0·5	26/8	0·6	64/28	Failed
261	0·5	32/12	0·6	52/34	Failed
172	0·6	36/20	0·7	68/46	Failed
152	0·8	64/48	Not reached	—	Success
182	0·6	38/22	0·7	84/44	Failed
193	0·9	0/0	1·0	40/32	Failed
16	0·9	28/16	0·95	16/8	Failed
204	1·3	84/44	1·4	86/44	Success
178	0·95	30/10	1·0	60/22	Failed
321	0·6	18/6	0·7	60/14	Failed
223	0·55	22/24	0·6	132/54	Failed
167	0·7	64/42	Not reached	—	Success
206	0·8	18/10	0·85	72/30	Failed
194	0·9	56/48	1·0	148/64	Failed
183	0·6	32/14	0·7	86/64	Failed
298	0·9	28/18	1·0	20/6	Failed
300	0·5	42/32	0·6	80/52	Success
305	0·9	28/18	1·0	128/82	Failed
318	0·6	20/12	0·7	82/40	Failed
320	0·6	8/2	0·7	70/24	Failed
325	0·5	46/21	Not reached	—	Success

nausea, and vomiting. Toxic manifestations were usually accompanied by a considerable fall in arterial pressure, frequently to systolic levels below 100 mm. Hg. In many cases no hypotensive effect was observed until toxic manifestations occurred. A precipitous fall in arterial pressure then followed, with faintness and hypotension when standing up. Faintness was rapidly overcome by lying down. Vomiting was frequently caused by food; a mid-morning cup of tea or occasionally lunch being followed by nausea and sometimes vomiting within a few minutes.

The effective oral dose of either neogermitrine, protoveratrine, or the mixed alkaloids was smaller if taken before food than if taken after a meal; doses that produced little effect when taken after a meal produced hypotension and sometimes toxic effects if taken fasting. We have found that if small doses are given before meals the effects of a given dose are more constant from day to day than are the effects of the larger doses required after food. This would appear to be due to more rapid and complete absorption when taken fasting.

In only one patient did any discrepancy appear between the effects of neogermitrine and those of protoveratrine or mixed veratrum alkaloids. In this patient (Case 202) no toxic manifestations occurred with neogermitrine, although with other preparations there was no difference between toxic and therapeutic doses. Control of the blood pressure in this patient proved to be transient

The Basal Blood Pressure as a Means of Predicting the Response to Veratrum

The relationship between basal blood pressure and results of treatment is summarized in Table IV. Reviewing the 65 patients who have taken one or more veratrum preparations, we noted that those with basal diastolic pressures of 100 mm. Hg or less have responded better than those

TABLE III

Effect on Blood Pressure of Oral Administration of Protoveratrine

Case No.	Maximal subtoxic dose (protoveratrine) (mg.)	Blood pressure fall	Toxic dose (mg.)	Blood pressure fall	Result of test
191	1·0	0/0	1·25	54/38	Failed
203	0·5	0/0	0·75	70/40	Failed
33	1·0	30/20	1·25	138/100	Failed
169	1·0	70/22	Not reached	—	Success
162	1·25	80/56	Not reached	—	Success
157	1·0	64/30	Not reached	—	Success
16	1·25	30/14	1·5	64/38	Failed
61	0·5	0/0	0·625	68/60	Failed
204	1·75	72/44	Not reached	—	Success
221	0·625	34/22	0·75	42/38	Failed
178	1·0	30/14	1·25	60/24	Failed
193	0·5	0/0	0·75	72/60	Failed
202	0·75	38/12	0·875	50/36	Failed
161	1·0	30/18	1·25	50/38	Failed
207	1·25	0/0	1·5	98/56	Failed
159	1·5	130/62	2·0	150/70	Success
152	1·25	76/39	Not reached	—	Success

with higher basal diastolic pressures. Of the 19 patients with basal diastolic pressures of 100 or below, 13 could be successfully treated. By contrast, none of the 32 patients with basal diastolic pressures above 120 could be successfully controlled for any length of time with veratrum alkaloids.

TABLE IV

Relationship Between the Basal Diastolic Blood Pressure and Control Achieved by Veratrum Alkaloids

Basal diastolic pressure	Successes	Failures	Total
Below 100	13	6	19
100–120	8	6	14
Above 120	0	32	32
Total number of cases ..	21	44	65

The Effects of Acute and Continued Administration

Trials of various oral doses indicate clearly those patients in whom a good fall in blood pressure cannot be produced without preceding or accompanying toxic manifestations. These patients form the majority of the present series. Attempts at continued treatment were made in all of the 21 patients who had a symptomless fall in blood pressure. It has been found, however, that toxic manifestations become more frequent after administration has been continued for periods of a month or more. The apparent narrowing of the margin between therapeutic and toxic effects appears to

occur to some degree in all patients with continued administration. In 11 of the 21 patients originally thought to be suitable for oral therapy, toxic manifestations became so frequent that treatment could not be continued.

Discussion

It has been shown that a very large fall in blood pressure can be produced by the intravenous administration of the pure veratrum alkaloids neogermitrine and protoveratrine, toxic effects occurring in about one-third of patients. A similar fall in blood pressure may be obtained by subcutaneous or oral administration of these alkaloids, but toxic effects occur in over two-thirds of patients. It would appear probable that the lower incidence of toxic effects when the intravenous route is used is due to the extremely accurate small doses; it seems that the margin between therapeutic and toxic effects is too narrow in most patients to enable successful subcutaneous or oral therapy to be used. Hence an intravenous test is not a guide to the value of prolonged subcutaneous or oral therapy.

Comparison between the effects of the pure alkaloids neogermitrine and protoveratrine on the one hand, and the mixed alkaloidal preparations on the other, indicates that the pure alkaloids cause toxic side effects almost as frequently as the less purified preparations. Hence it appears likely that the toxic effects of the mixed alkaloidal preparations are not due to the presence of contaminating constituents, but are caused mainly by the alkaloids themselves.

The level of the basal diastolic pressure seems to afford some indication of the chance of obtaining a good fall in blood pressure without toxicity, since about two-thirds of patients with low basal diastolic pressures could be effectively treated. Freis and Stanton (1948) gained the impression that patients with high diastolic pressures responded as well as the early mild cases. The difference between their results and ours might be due to the fact that we have aimed at greater reduction in blood pressure.

Tests undertaken with inert control substances have demonstrated that considerable falls in blood pressures may occur spontaneously, especially in patients with low basal blood pressures. Hence, great care must be taken in the interpretation of the blood pressure falls obtained following the administration of any hypotensive drug which is being tested. We are confident, however, that the falls in blood pressure that have been observed in patients with labile hypertension following the administration of the veratrum alkaloids are greater and more consistent than those obtained by the administration of a placebo.

Summary

Minute doses such as 0·1 mg. of neogermitrine or 0·15 mg. of protoveratrine, when given intravenously in hypertensive patients, produce falls of blood pressure to normal or even to hypotensive levels. Rather larger doses (0·4 mg.) given subcutaneously or orally have similar effects.

The therapeutic margin between toxic and hypotensive doses is not distinctly greater with the pure alkaloids than with mixed alkaloidal preparations. The alkaloids that lower the blood pressure also lead to the characteristic toxic manifestations.

The blood pressure may be reduced more readily without toxic symptoms in labile than in fixed hypertension.

Toxic effects have been less frequent when the veratrum alkaloids have been given in small subdivided doses intravenously than when administered by mouth or subcutaneously. An explanation is discussed.

Of 65 hypertensive patients in whom veratrum treatment has been attempted here, a good measure of control over the level of the blood pressure has been possible in about 15. Although a good control over the blood pressure can be obtained for a time in a larger number of patients, the margin between therapeutic and toxic doses narrows and effective treatment cannot be maintained in all patients who began well.

We are indebted to Mr. W. G. H. Edwards of the Chemistry Department, University of Otago, for the isolation of neogermitrine; to Dr. O. W. Chapman, Assistant Physician, Dunedin Hospital, for permission to quote some of the cases reported in an earlier publication; to Miss J. Rivers for technical assistance; and to Miss M. Popplewell for secretarial assistance.

The following firms have given generous supplies of materials:—anatensol from Messrs. E. R. Squibb & Sons, New York, N.Y.; vertavis from Messrs. Irwin, Neisler & Co., Decatur, Ill.; protoveratrine from Riker Laboratories, Inc., Los Angeles and Messrs. Eli Lilly & Co., Indianapolis, Ind.

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CASE REPORTS

A CASE OF ENDOCARDIAL FIBROSIS SHOWING HEPARIN-RESISTANCE

BY

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Endocardial fibrosis has recently been reviewed by Gray (1951) and in a *Lancet* annotation (1952). The myocardial lesions of this disease are very similar to those following arsenical dermatitis (Brown and McNamara, 1940), scarlatina, and sulphur ointment dermatitis (Brody and Smith, 1936), thus suggesting allergy as an ætiological factor. Abrahams *et al.* (1949, 1951) demonstrated heparin-resistance in rheumatic fever—a disease widely regarded as allergic in origin. In the case reported here a similar resistance to the action of heparin was demonstrated; furthermore, aortic hypoplasia and eosinophilia were absent, and connection with the tropics so remote as probably to be of no significance. Pulmonary infarctions were believed to follow thrombosis in the pulmonary arterial tree rather than embolism.

Case Report

A married man, aged 54, railway porter, was admitted to the Professorial Medical Unit, Maryfield Hospital, Dundee, on 16/8/51. Following a clinical episode of myocardial infarction in 1949, he had been breathless and able to perform only light work. Two weeks before admission, when at rest, he first felt pain over the left lower ribs in front, but spreading occasionally across the chest. It began gradually and was accompanied by breathlessness which increased in severity until on admission he was dyspnœic at rest.

Past history. Apart from service in Macedonia in the 1914–18 war he had not been in tropical or sub-tropical countries. He had then contracted malaria (1916)—a single attack with no relapses.

Examination on admission. The temperature was 100·5° F., the pulse 110 a minute, respiration 24 a minute. He was cyanosed and orthopnœic, with raised venous pressure, liver enlargement, and œdema. The blood pressure was 118/80. Frequent extrasystoles were present. There was cardiac enlargement, the apex beat being tapping in quality and situated 3·7 cm. outside the mid-clavicular line. No murmurs were heard but the second sound was widely split in all areas. Crepitations were present at both lung bases.

Blood. E.S.R. 20 mm. in 1 hr. (Westergren). Hb. 104 per cent (14·4 g. per 100 ml.), R.B.C. 4 million and W.B.C. 12,000 per cu. mm.; differential white count normal—no eosinophilia. W.R. negative. Blood cultures (broth) negative on four occasions.

Cardiogram on 21/8/51 showed a right axis deviation and a vertical heart, abnormal P waves in leads II and V1, P–R interval of 0·2 sec., QRS of 0·12 sec., low voltage T waves, and a pathological Q wave in V5 suggesting an old anterolateral infarct (Fig. 1A).

Chest X-ray showed generalized cardiac enlargement with cardiothoracic ratio of 72 per cent and pulmonary congestion.

The *urine* was chemically and microscopically normal.

Progress

Intramuscular heparin administration was begun on admission and continued for seven days. Prolongation of clotting times (by Lee and White's method) did not follow the usual therapeutic doses. For example, on the first day at 6 p.m. the clotting time was 4 minutes; 25,000 units of heparin were then injected; at 9.15 p.m. the clotting time was only 5 minutes and at 6.30 a.m. on the next morning, it was 5½ minutes. Again, on the third day 25,000 units of heparin at midnight was followed by a clotting time of only 6 minutes at 6.30 a.m., while on the sixth day, following the same dose at midnight, the 6.30 a.m. clotting time was only 8½ minutes, which was the longest time recorded. Tromexan was then given for five weeks. In spite of adequate reduction in prothrombin levels (between 10 and 30% throughout), four further attacks of chest pain occurred accompanied on each occasion by blood in the sputum. These episodes suggested repeated pulmonary infarctions. On 1/10/51 heparin therapy was started again and on this occasion a normal response was obtained. For example, with a control clotting time before heparin of 8 minutes,

12,500 units intra-muscularly produced clotting times of 22 and 32 minutes, 4 and 8 hours respectively after the injection. Thereafter, for seven days, the clotting times were easily maintained between 18 and 56 minutes by daily doses not exceeding 25,000 units. In spite of this, another myocardial infarction occurred on 4/10/51; the electrocardiogram was confirmatory, showing S–T shift in V3 and further prolongation of the P–R interval (Fig. 1B).

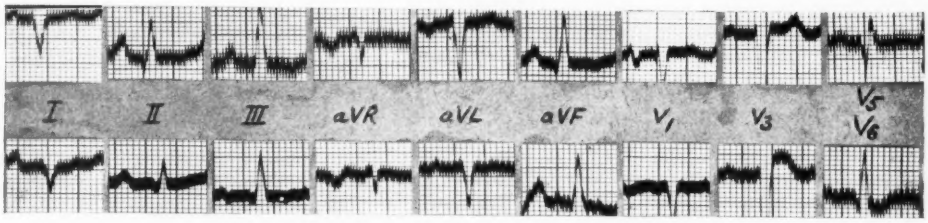

FIG. 1.—(A) Electrocardiogram on 21/8/51 showing evidence of the anterolateral infarction. (B) Record on 4/10/51 showing evidence of further myocardial infarction.

Low-grade pyrexia in association with the attacks of chest pain did not respond to chemotherapy and antibiotics. Œdema increased in spite of administration of digitalis, squill, low-sodium diet, kation exchange resin, and mercurial diuretics, until eventually it required drainage. The congestive failure was intractable, and in this way the patient's condition gradually and progressively deteriorated until death occurred on 18/11/51, three months after admission to the ward.

Post-mortem Examination

The heart was enlarged and globular and weighed 616 g. Diffuse fibrosis throughout the myocardium was most pronounced in the sub-endocardial zone. A fairly recent infarction of the anteroseptal wall of the left ventricle and two older infarctions of the posterior wall were present (Fig. 2). Although gross atheroma

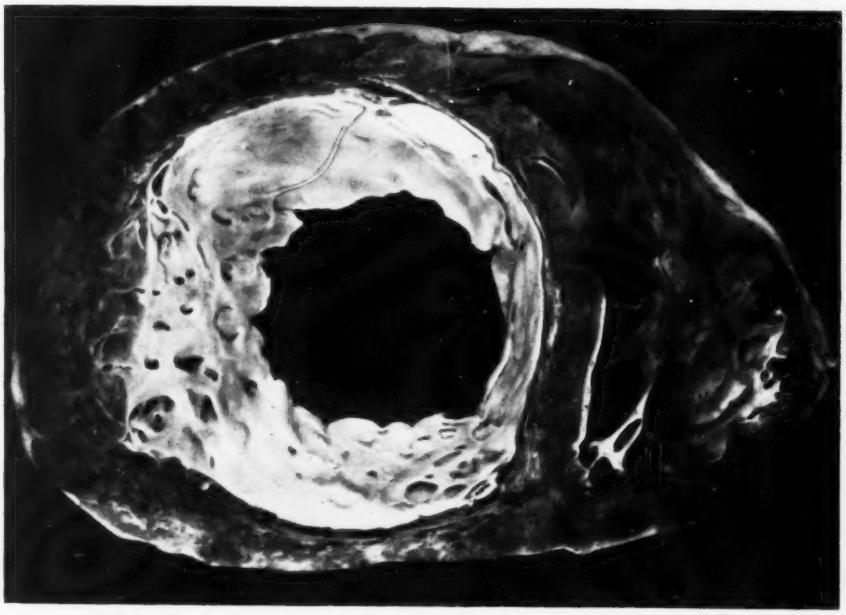

FIG. 2.—Transverse section of heart viewed from above showing interior of left and right ventricles and endocardial fibrosis.

of the coronary arteries was found, there was no evidence of thrombosis in the branches. All four heart chambers contained organizing mural thrombi; the endocardium of the left auricle and ventricle was very thick (2·0 mm.), white and opaque. Similar changes were present in much less degree in the cavities of the right side of the heart. The tricuspid valve was normal; atheromatous deposits were seen on the pulmonary valve and in the pulmonary trunk. The cusps of the mitral valve were thickened and opaque and this thickening extended along the chordæ tendineæ to the papillary muscles. The aortic valve was competent but showed several warty deposits upon the ventricular aspect of its mitral cusp. The aorta was normally developed and showed no evidence of hypoplasia. Microscopic examination of the left ventricle showed gross fibrous thickening of the endocardium and fibrous replacement of muscle. The latter was most pronounced in the sub-endocardial region except for a band of muscle tissue which seemed to have escaped destruction. Generally, the myocardium showed irregular bands of fibrous tissue spreading for varying distances between muscle bundles and in places compressing them. This gross increase in connective tissue together with patchy lymphocytic infiltration resembled a chronic inflammatory process (Fig. 3). The areas of infarction showed the usual appearances, compatible with the age of the lesion.

FIG. 3.—Section of the left ventricular myocardium showing interstitial fibrous replacement of muscle and areas of lymphocytic infiltration.

Both lungs contained multiple infarcts of varying size, some old and in various stages of organization, others recent and hæmorrhagic. One very large hæmorrhagic infarction was present in the posterior part of the right upper lobe, apparently caused by thrombosis of a large branch of the pulmonary artery. The pulmonary arterial tree was grossly atheromatous and there was no doubt that some of the infarcts were due to antemortem intra-arterial thrombosis and were not of embolic origin.

Summary

A case of endocardial fibrosis showing heparin-resistance and some other features is reported. Necropsy showed infarctions in the heart and in the lungs. In the latter situation they were believed to be due to thrombosis in the pulmonary arterial branches.

We are grateful to Professor Ian G. W. Hill for his invaluable help and advice.

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ISOLATED DIFFUSE MYOCARDITIS

BY

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Evans (1949) has described a syndrome having a clinical, cardiographic and pathological pattern that he has named familial cardiomegaly. The following case is reported because it is representative clinically and cardiographically, and yet showed a different pathological picture from that expected.

Report of Case

A man, aged 20, came under observation at the West London Hospital in June, 1946; he was then 20 years of age. He complained of attacks of giddiness and unconsciousness of short duration, present for eight months. For two months he had had a sharp retrosternal pain accompanied by palpitation on exertion, relieved by rest. There were no other symptoms. He gave a history of rheumatic fever at the age of 7 years, when heart disease was diagnosed. There was a striking family history of heart disease and early death. A maternal great aunt dropped dead in the street at the age of 19. Four aunts and uncles died cardiac deaths between the ages of 23 and 40 and four others of this line died during infancy of what was said to have been heart disease. Abnormal physical signs were limited to the cardiovascular system. The pulse was irregular from premature beats. The left side of the chest was more prominent than the right. The apex beat was situated in the fifth space one inch outside the midclavicular line. The cardiac impulse was forcible. A presystolic triple rhythm was present, and there was a soft blowing systolic murmur at the apex conducted towards the axilla. The blood pressure was 120/70. There were no basal râles; neither the liver nor spleen was palpable. The central nervous system was normal. X-rays and fluoroscopy demonstrated great enlargement of the heart, particularly of the left ventricle. The electrocardiogram showed ventricular premature beats, tall wide P waves, inversion of T in leads I and II with diphasic T in IV R, and depression of S–T in these leads. The blood count, sedimentation rate, blood cholesterol, and sugar tolerance curve were all normal. There was no fever.

During the next three years he suffered remarkably little disability and led a fairly normal life. There were several attacks late in 1946 of severe substernal pain radiating to the arms accompanied by sweating and vomiting, but not by rise in temperature or sedimentation rate or change in the electrocardiogram. Syncopal attacks occurred irregularly throughout the whole period. The pattern of a left bundle branch block developed. Finally he became dyspnœic on exertion and coughed up blood on several occasions. A well marked third heart sound, and sometimes a fourth, became audible. Death in June, 1949, was preceded by a prolonged bout of paroxysmal tachycardia (Fig. 1).

Summary of Necropsy

Heart failure, isolated myocarditis, and bronchopneumonia. The heart weighed 820 g. The pericardium was adherent over the anterior, lateral, and posterior aspects of the left ventricle and also to the diaphragm. The adhesions were tough and vascular at one point. There were 150 ml. of fluid in the pericardial sac. The heart was pale, and there were many petechial hæmorrhages. There was a fibrous patch 2·5 by 1·2 cm. in the right ventricle. Both ventricles were enlarged; the left was thick and tough and the right was flabby. The aortic cusps were healthy. The right ventricular wall was 5 mm. thick. At the junction of the upper one-third and lower two-thirds of the organ the septum measured 2·5 cm. in thickness and the left ventricle 2·5 cm. The left ventricular wall was enormously hypertrophied, and fibrous towards the apex anteriorly. The mitral valve was normal, and the left atrium was a little dilated. There was roughening on the margin of the

mitral valve and patches of atheroma around the right coronary orifice. The coronary arteries were healthy but small compared to the thickening of the left ventricle. There was diffuse fibrosis over the caudal end of the septum and apex, and adhesions over the posterior aspect.

The great vessels showed no abnormality. The lungs were congested with patches of bronchopneumonia. The liver was congested and there was a marked degree of nutmeg appearance. The spleen weighed 370 g. There were no abnormalities elsewhere.

Microscopic examination of the heart. In all parts examined there was dense patchy fibrosis of the myocardium, present also beneath the endocardium; the muscle fibres were hypertrophied. There was a scattered cellular infiltrate consisting of lymphocytes and mononuclear cells (Fig. 2).

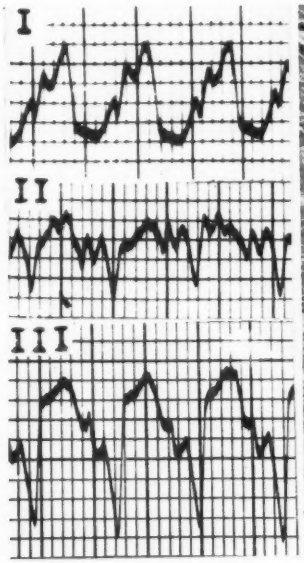

FIG. 1.—Electrocardiogram showing pattern of paroxysmal tachycardia. Time intervals 1/5 and 1/25 second.

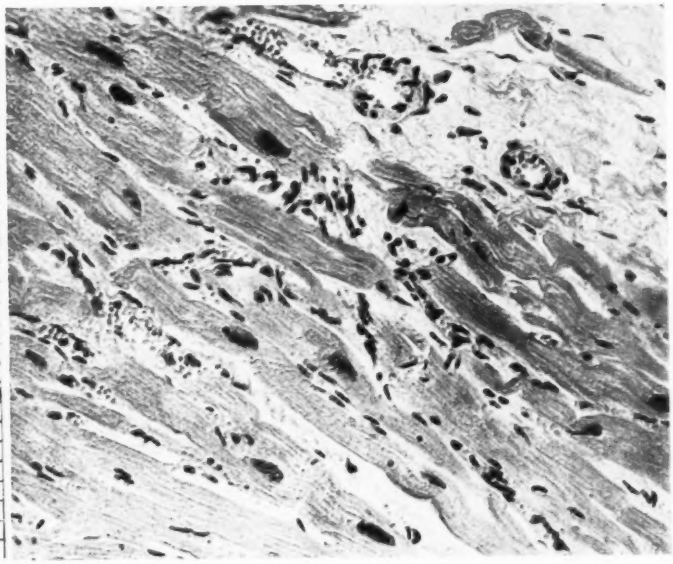

FIG. 2.—Microscopical section of the myocardium showing fibrosis, muscular hypertrophy, and cellular infiltrate. H and E, ×1/290.

No Aschoff bodies were seen. The sections were examined by Dr. C. V. Harrison of the Postgraduate Medical School, University of London, who reported: " This is an example of a smouldering, almost healed myocarditis. The fibrosis is not of the type or distribution which one sees in either rheumatism or ischæmia and there is endarteritis in small arteries and still some cellular infiltration in the interstitial tissue. The myocardial hypertrophy could, I think, be due simply to the long-continued myocardial failure resulting from the inflammatory myocarditis "

Discussion

It is reasonably clear that we are dealing with an instance of late isolated diffuse (Fieldler's) myocarditis (Saphir, 1942*b*). Whether this man really had rheumatic fever at the age of seven we do not know, but the present pathological findings are not those of rheumatism. Aschoff nodes are necessary to make the diagnosis in the absence of typical valvular lesions (Saphir, 1941 and 1942*a*). Pericardial adhesions may or may not be a cause of cardiomegaly (Wolfe, 1950), but were hardly sufficiently severe to have caused it here, in addition to which there is ample cause for both the adhesions and the cardiac enlargement in chronic inflammation. The Wassermann reaction is not

available, but syphilis may be confidently excluded as the cause. Syphilitic myocarditis is very rare, is gummatous, and may only be diagnosed if typical gummata are found or treponemata demonstrated (Saphir, 1942*a*).

Whether there is any relationship between idiopathic hypertrophy and chronic myocarditis is at the moment a matter for conjecture. Some authors (Jones and Marshall, 1948; Ware and Chapman, 1947; Sellers and Phillips, 1946) have postulated that hypertrophy with fibrosis without cellular infiltrate may be the end result of a healed chronic myocardial inflammation. That the two may not always be easy to differentiate is well shown in a case report from the Massachusetts General Hospital (1951) though the microscopic findings may have been altered by cortisone therapy. It is more difficult to link up a familial history of heart disease with inflammatory findings, and little will be gained at present by speculation. A case report similar to this in many ways was published by Addarii *et al.* (1946) though the evidence of inflammation was very slight.

Summary

A case is reported that corresponds clinically and cardiographically to the syndrome of familial cardiomegaly, but had, at autopsy, the findings of a late isolated diffuse myocarditis.

I wish to thank Dr. G. L. S. Konstam for allowing me to record this case and Dr. Richard Pearce together with Dr. C. V. Harrison for their pathological reports. I am grateful to Mr. H. G. Blunt for providing slides and photographs.

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RUPTURE OF AN AORTIC ANEURYSM INTO THE PULMONARY ARTERY

BY

G. H. JENNINGS

From the Edgware General Hospital

Since ligation of a patent ductus arteriosus is now a popular and effective operation, it is of practical interest to consider other cardiac conditions that, by producing a similar murmur, may lead to a pre-operative error in diagnosis. If the " mill-wheel " or " machinery " murmur of patent ductus arteriosus has not fully developed, the error may be one of oversight, but confusion may also arise when a similar murmur is produced by other defects. These defects all include a free leak from the aorta above the cusps, and may be either congenital or acquired. If the defect be one in the aortic septum, the murmur may date from birth, and in such a case the expectation of life is not above fourteen years (Dadds and Hoyle, 1949). A similar murmur may follow rupture of a congenital aneurysm of the sinus of Valsalva into the pulmonary conus and may occur at twelve years or not until the patient is over forty years of age (Morgan Jones and Langley, 1949). These authors also described similar rupture of two acquired sinus aneurysms, one possibly due to rheumatism, but the best recognized acquired lesion to produce the mill-wheel murmur is a fistula between a syphilitic aneurysm of the first part of the aortic arch and the pulmonary artery. The following description is of a case of this kind.

Case Report

History. A factory manager, aged 44 years, was admitted with a history of very good health and good athletic record till two years previously. He then began to notice slight dyspnœa on exertion, which increased gradually till two months before his admission, when he became much more dyspnœic at all times and was in particular subject to acute attacks of dyspnœa at night. A few nights before admission he had severe vomiting, and when admitted he was still trying to make himself vomit and occasionally succeeded in raising a little blood-tinged sputum. He was very nervous and worried, and complained of severe epigastric tightness and discomfort.

Physical examination. A well developed, muscular man, afebrile, orthopnœic, markedly dyspnœic and moderately cyanosed. The neck veins were filled nearly to angle of jaw and pulsated visibly. The *heart* showed a rather diffuse apical impulse just external to the nipple line in the fifth left space. A loud systolic and diastolic " mill-wheel " murmur was heard all over the præcordium, loudest in the pulmonary area, where it was accompanied by a synchronous palpable thrill. The heart rate was at 116 a minute. The blood pressure was 130/50. The left base showed many râles, and a moderate pleural effusion covered the right base and lower axilla.

The liver was tender and smooth, extending 8 cm. below the right costal margin. Moderate œdema of sacrum, feet and ankles was present.

Investigations. An X-ray of the chest showed much dilatation of the pulmonary artery and conus, and heavy shadows of the pulmonary branches, with some congestion of the lung bases (Fig. 1).

An electrocardiogram showed sinus tachycardia and a tendency to right axis deviation. Lead I showed a good voltage RS and lead III a prominent Q and high R waves. T waves were upright in leads I and II, and showed shallow inversion in lead III. In CR4, the R wave was of low voltage and the S wave deep. A raised S–T segment and shallow inversion of the T wave, also present in this lead, were attributable to myocardial ischæmia resulting from the narrowed coronary ostia (Fig. 2).

The blood Wassermann reaction was positive (++).

FIG. 1.—Ward Unit X-ray of chest showing no evidence of aortic aneurysm, but considerable distension of the pulmonary artery and congestive hyperæmia of the lungs.

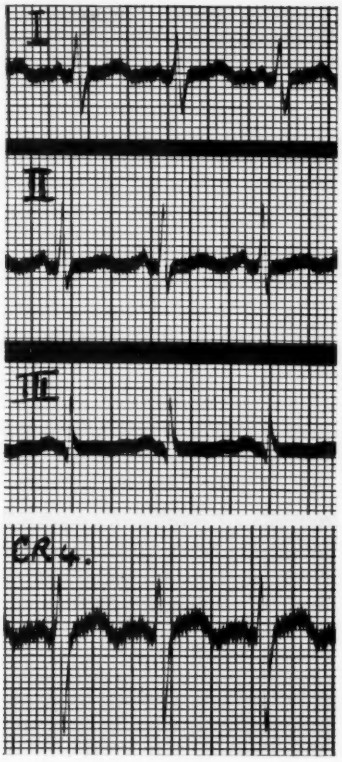

FIG. 2.—Electrocardiogram showing tachycardia and slight tendency to right axis deviation in the standard leads. Chest lead CR4 shows raised S–T and slightly inverted T wave due to the myocardial ischæmia resulting from narrowing of the coronary ostia.

Progress. The patient's condition steadily declined in the next two weeks, and despite gastric lavage he continued to retch. Further accumulation of fluid at the right base and increased dyspnœa necessitated aspiration of two pints of blood-stained pleural fluid, but he remained very ill and the neck veins continued to show free pulsation. Increasing weakness and drowsiness preceded his death on the thirteenth day in hospital.

Necropsy (Dr. J. L. Hamilton Paterson). Heart enlarged, with hypertrophy of both ventricles; valves competent; pericardium normal; myocardium firm and reddish in colour. The ascending part of the aorta showed a saccular aneurysm which anteriorly had pressed against the pulmonary artery. Here the sac wall had been thinned with resulting perforation into the pulmonary artery immediately above the semilunar (tricuspid) valve. The aneurysm showed much irregular thickening and fibrosis of the aortic wall, suggestive of syphilitic nature; the coronary ostia, particularly the left, were narrowed by the disease. The perforation was 6 mm. in diameter and roughly triangular in shape. All the lobes of the lung showed an intense œdema. The liver showed advanced nutmeg change with early nodular hypertrophy.

Discussion

The rupture of syphilitic aneurysms is usually into the main pulmonary trunk, as in the case just described, but one case of two reported by Schattenburg and Harris (1943) ruptured into the

left pulmonary artery. These writers estimated that upwards of sixty cases had been described by 1943, the first by Wells in 1812 (quoted by Peacock), and the first full clinical description by Hope in 1839. Wade (1861) made the first clinical ante-mortem diagnosis, and in 1868 there were two excellent clinical accounts of cases by Murchison and by Peacock, the latter also giving an up-to-date summary of thirty-three cases of thoracic aortic aneurysms perforating the cavities of the heart and of the adjacent great vessels. Eighteen of these were from the sinuses of Valsalva and twelve from the first part of the aortic arch. In his case Roberts (1869) was struck by the superficiality of the murmur thus foreshadowing a similar observation made by Maude Abbott (1937) on the murmur of aortic septal defect.

A rarer mode of rupture of an aortic aneurysm is into one of the larger thoracic viens, and Danaray's (1949) account of a Chinese labourer who suffered this accident reveals its catastrophic nature: within twenty-seven hours of sudden severe pain across the chest, the patient had died after developing severe dyspnœa, cyanosis, engorgement of neck veins and a swollen neck; he showed a widespread præcordial machinery murmur. A similar type of murmur of congenital origin is described by Biörck and Crafoord (1947), who found at operation an aneurysm on an aberrant coronary artery opening into the main pulmonary artery.

The close apposition of pulmonary artery and aorta may cause a quite small syphilitic aneurysm to perforate into the pulmonary artery as a result of pressure erosion. This was so in our case, in two of Peacock's cases, and also in Roberts' case, where the aneurysm was " half the size of a walnut shell." An erosive opening appears usual, but Peacock quotes examples of aneurysms that " lacerated " into the pulmonary artery with correspondingly worse prognosis. Osler and McCrea (1936) state that rupture may cause instantaneous death, but, on the other hand, death may not follow perforation for twenty-one months (White *et al.*, 1941). Porter (1942), after observing three cases, considered that the time of survival depended both on the size of the fistulous opening and on the amount of associated cardiovascular disease. Our case emphasises the fact found in others previously reported that perforation may not be accompanied by præcordial pain; sensations of " chill " and increasing dyspnœa are often the main initial symptoms. It also shows the importance of catastrophic cardiac failure and a positive Wassermann reaction in making full assessment of a case where a mill-wheel murmur is present, for in it neither radiography nor electrocardiography gave distinctive findings.

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A CASE OF PAROXYSMAL SUPRAVENTRICULAR TACHYCARDIA IN INFANCY TREATED WITH PROCAINE AMIDE

BY

N. SHER

From the Booth Hall Children's Hospital, Manchester

Paroxysmal rapid heart action in infancy is not common. The condition is sometimes difficult to recognize as it may be symptomless or may only be detected during examination for a complaint unconnected with the cardiovascular system. However, its recognition is important because the response to therapy is satisfactory and may, on occasion, be life-saving. The following case is reported to illustrate this.

A male infant, aged 2 months, was admitted to Booth Hall Hospital, Manchester, with a two-day history of fever, coryza, and cough. The infant had been born with asphyxia livida due to the cord round the neck but resuscitation was successful. He was not breast-fed and thrived on a dried milk formula.

On examination he was a well nourished infant, apyrexial but very dyspnœic with a respiratory rate of 60 a minute. There was no cyanosis or œdema. The pulse and heart rate seemed too fast to count with accuracy. The liver at this stage was not palpable and a diagnosis of upper respiratory infection was made. During the next day, the infant's condition deteriorated and signs of cardiac failure became evident, with cyanosis, congestion of the neck veins, peripheral œdema, and enlargement of the liver to four finger breadths below the costal margin. The heart rate was still difficult to count and a diagnosis of paroxysmal tachycardia with cardiac failure was made.

An injection of 50 mg. of procaine amide hydrochloride (pronestyl) was given intravenously and the heart rate fell immediately to 168 a minute but in the next eight hours the rate rose again and once more became uncountable. A further intravenous injection of 50 mg. pronestyl was given, but on this occasion it had no effect. Digoxin 0·25 mg. was then given orally and within two hours a decided improvement in the infant's condition was noted, and in four hours the heart rate was reduced to 180 a minute. The digoxin was continued orally four-hourly in the same dosage for the next 24 hours. By this time the cyanosis and œdema had gone and the liver edge was just palpable below the costal margin, the heart rate being 140. The dose of digoxin was then reduced to 0·125 mg. eight-hourly, and the pulse gradually fell to 98 a minute. After a further four days the digoxin was discontinued. An electrocardiogram taken at the end of the treatment showed a regular rate of 125 with a P–R interval of 0·08 sec. and a QRS duration of 0·06 sec. All waves were of normal configuration and the infant was discharged well after a further 14 days.

However, four months later he was readmitted, now aged six months, with a history of breathlessness, oliguria, and vomiting for 24 hours. On examination cyanosis and dyspnœa were noted. There was no œdema, and the liver was once again palpable four finger breadths below the costal margin and once again the heart rate was very fast and estimated to be over 200 a minute. Paroxysmal tachycardia was diagnosed and an electrocardiogram was taken (Fig. 1) which showed a regular heart rate of 270. The P waves were upright in the standard leads and there was a short P–R interval of 0·08 sec. and a short QRS duration of 0·05 sec., confirming the diagnosis of supraventricular paroxysmal tachycardia of sinus origin. An X-ray also showed enlargement of the cardiac silhouette.

A dose of 50 mg. of procaine amide hydrochloride (pronestyl) was then injected into the superior sagittal sinus. The heart rate was immediately reduced to 230 but 20 minutes later it was uncountable again. After 3 hours the infant's condition was much worse and a further 75 mg. pronestyl was given intravenously with an immediate reduction of the heart rate to 144 a minute. The pulse rate continued to fall and three hours after the second injection it was 120 and 12 hours later was 100. The rate remained between 100–120 without further treatment. The child's condition improved rapidly, the cyanosis and signs of congestive failure disappeared six hours after the last injection of pronestyl. The liver gradually receded and two days after treatment was one finger breadth below the costal margin. An electrocardiogram (Fig. 2) taken 12 hours after the second dose of pronestyl showed the heart rate to be 130 but the P waves, P–R interval, and QRS interval were unchanged. The infant continued to be well till his discharge seven days after admission, and during the past six months had had no further paroxysms.

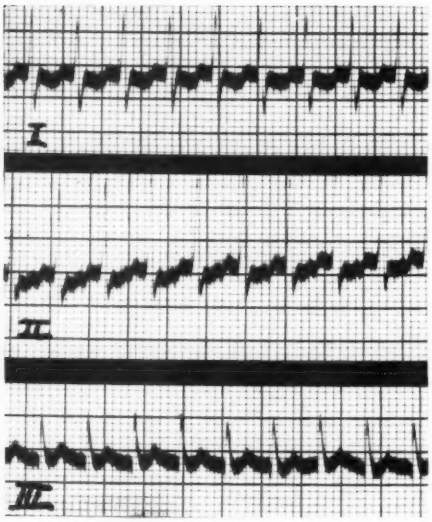

FIG. 1.—Electrocardiogram showing paroxysmal tachycardia, rate 270 a minute.

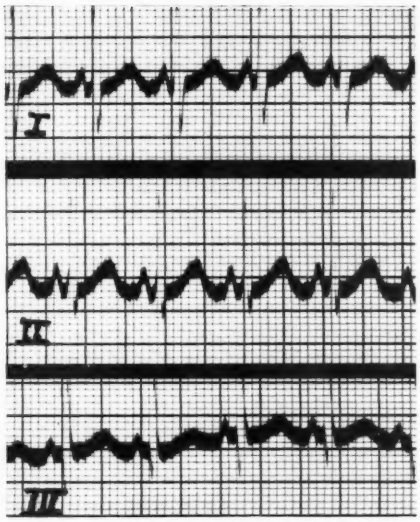

FIG. 2.—Electrocardiogram taken 12 hours after second dose of pronestyl, showing return of sinus rhythm.

Discussion

Procaine amide, the synthetic analogue of procaine, has been found to have potent anti-arrhythmic properties. Its action is not, as yet, fully understood, although it is known to have an effect similar to that of quinidine and prolongs the refractory period of heart muscle. Kayden *et al.* (1951) recommended intravenous administration in adults at a rate of 200 mg. a minute until a total of 1 g. has been given, while orally a single dose of 1·25 g. followed by 0·75 g. in one hour was effective. McCord and Taguchi (1951) have employed this drug in three cases of paroxysmal supraventricular tachycardia with reversal to normal sinus rhythm in each case, while Berry *et al.* (1951) have had good results in 22 cases of nodal and auricular tachycardia with only 4 failures. More recently, serious toxic effects have been reported following the use of pronestyl, and Read (1952) reported a death from ventricular tachycardia in a woman of 61 years after an intravenous dose of 200 mg., while pyrexia and a macular rash have also been reported by Bakos and Askey (1952) and Hellman (1952). Digoxin and pronestyl are equally successful in the treatment of paroxysmal tachycardia, but if any advantage can be claimed for pronestyl, it is its rapidity of action, which is almost immediate, while the first effects of digoxin are not noted for about two to four hours. The dose of procaine amide in infants is not known, but in the case reported 110–132 mg. per kg. body weight was effective. It is possible that if a larger dose of pronestyl had been given at the outset, one intravenous injection only might have been necessary. It is interesting to note that the pronestyl had no effect in lengthening the P–R interval or the Q–T interval. Further trials with this drug must be carried out before its place in the treatment of the cardiac arrhythmias can be assessed and future developments are awaited with interest.

Summary

A case of paroxysmal supraventricular tachycardia in infancy is described. Two intravenous doses of procaine amide hydrochloride totalling 125 mg. brought the paroxysm to an end.

I am grateful to Dr. W. H. Patterson, Medical Superintendent, Booth Hall Hospital, for his advice.

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PROCEEDINGS OF THE BRITISH CARDIAC SOCIETY

The THIRTY-SECOND ANNUAL GENERAL MEETING of the British Cardiac Society was held at the Royal Victoria Infirmary, Newcastle-upon-Tyne, on Thursday, May 21, 1953. Chairman: SIR WILLIAM HUME. The Chairman took the Chair at 9.30 a.m.; 110 members and 24 visitors were present.

PRIVATE BUSINESS

1. The minutes of the last Annual General Meeting, having been published in the Journal (**14**, 541, 1952) were taken as read and confirmed.

2. The balance sheet for 1952–53 was presented, having been audited and found correct by J. L. Lovibond and J. H. Wright. The credit balance on May 5, 1953, was £378 11*s.* 11*d.*

3. Professor Gustav Nylin was elected and acclaimed as an Honorary Member of the Society.

4. T. H. Crozier and G. W. Hayward were elected members of the Council in place of J. L. Lovibond and C. Bruce Perry (terms of office expired).

5. The following Associate Members were elected as *Ordinary Members.*

G. Aitken	T. E. Gumpert	I. Macpherson
D. R. Allison	R. Hartley	J. P. Shillingford
H. A. Dewar	H. E. Holling	A. J. Thomas
J. F. Goodwin	F. Jackson	A. J. Wilson

6. The following *Associate Members* were elected for a further period of three years.

W. H. R. Cook	R. W. Luxton
R. Byron Evans	H. E. S. Pearson

7. The following new *Associate Members* were elected and introduced.

C. D. Anderson (Glasgow)	H. Scarborough (Cardiff)
R. E. Benson (London)	H. J. Wade (Manchester)
C. E. Davies (Sheffield)	W. Whitaker (Sheffield)
R. Hudson (London)	A. G. W. Whitfield (Birmingham)
D. H. Makinson (Bangor)	M. Zoob (London)
E. Lawson McDonald (London)	

8. It was proposed and accepted that Rule 4 of the Society should read as follows.
" There shall be a President of the Society who shall be nominated by the Council and elected by the Society. He shall be elected for two years and may be eligible for re-election for a further period of two years on the recommendation of the Council. He will be *ex officio* a member of the Council. He may preside over meetings of the Council but not at the Scientific Meetings of the Society, for which a local Chairman will be elected annually."

9. It was proposed and accepted that Rule 7 of the Society should read as follows.
" Ordinary and Associate Members shall not exceed 225 in number. This includes up to 15 Ordinary or Associate Members who may be elected for their interest in cardiovascular surgery."

10. It was decided that the Autumn Meeting of the Society should be held in London in November, 1953, and that the programme should consist of short communications.

11. It was decided that the Annual General Meeting of the Society, in 1954, should be held at Cambridge.

12. The following *Corresponding Members* were proposed and elected.

Professor Rijlant (Belgium)
Dr. Van Dooren (Belgium)
Professor Lequime (Belgium)
Professor Warburg (Denmark)
Professor Soulié (France)
Professor Froment (France)
Professor Lenègre (France)
Professor Heim de Balsac (France)
Professor Wollheim (Germany)
Professor Formijne (Holland)
Dr. Snellen (Holland)
Professor Agostoni (Italy)
Professor Condorelli (Italy)
Dr. Puddu (Italy)
Professor Porto (Portugal)
Dr. Codina-Altés (Spain)
Dr. Biörck (Sweden)
Dr. Duchosal (Switzerland)
Dr. Mahaim (Switzerland)

From Canada

Dr. J. Hepburn (Toronto)
Dr. F. A. L. Mathewson (Winnipeg)
Dr. J. H. Palmer (Montreal)
Dr. G. F. Strong (Vancouver)

From Australasia

Dr. C. R. Burns (Wellington)
Dr. Clive Fitts (Melbourne)
Dr. E. F. Gartrell (Adelaide)
Dr. G. Lendon (Adelaide)
Dr. T. E. Lowe (Melbourne)
Dr. J. K. Maddox (Sydney)
Professor F. H. Smirk (Dunedin)

From South Africa

Professor W. H. Craib (Port Elizabeth)
Dr. H. L. Heimann (Johannesburg)
Dr. M. Suzman (Johannesburg)

Short Communications

The Frequency of Different Types of Congenital Heart Disease

By Maurice Campbell. From September, 1947, till the end of 1951, 1130 cases of congenital heart disease were studied and this deals with a preliminary analysis. It provided no evidence of the relative incidence of cyanotic and acyanotic disease because it is weighted by the former wanting operations, but in other particulars should be representative, except that there were relatively few children under three years of age. Three-fifths were cyanotic and two-fifths acyanotic (670 and 460). There are, no doubt, errors of diagnosis but as about 350 have had operations, and catheterization and angiocardiography have each been carried out in about 250, and the results of 120 necropsies are available, they should not be very numerous.

The acyanotic cases can be divided into five roughly equal groups—patent ductus arteriosus, 22 per cent; ventricular septal defect, 21 per cent; atrial septal defect, 18 per cent; coarctation of the aorta (7%) and aortic stenosis (11%) making 18 per cent; and pulmonary valvular stenosis, 16 per cent. The structure of the cyanotic group is quite different as 66 per cent had Fallot's tetralogy, including about 9 per cent with pulmonary atresia; 8 per cent had transposition of the aorta and pulmonary trunk; 6 per cent had pulmonary valvular stenosis with a right to left shunt; 6 per cent had Eisenmenger's complex; 5 per cent had tricuspid atresia; and the final 9 per cent had various anomalies including those with dextrocardia, lævocardia, and Ebstein's disease.

As expected, there was a considerable excess of males in coarctation (3 to 2) and in aortic stenosis (3 to 1), and of females in patent ductus arteriosus (2 to 1). There was no significant difference in the other acyanotic groups. Rather surprisingly this was true for atrial septal defect, but in those over 25 there was the expected preponderance of women (5 to 1).

In the cyanotic group, Fallot's tetralogy and transposition showed male preponderance (3 to 2) and Eisenmenger's complex female preponderance (2 to 1).

It is doubtful what conclusions can be drawn from the age incidence because children preponderate in all groups.

There is a striking contrast between the slight mortality in the acyanotic and the very heavy mortality in the cyanotic groups, quite apart from the operative deaths. In pulmonary atresia this amounted to nearly 40 per cent; in tricuspid atresia and in transposition of the main vessels to 30 per cent; in pulmonary valvular stenosis with a right to left shunt to 20 per cent; and even in Fallot's tetralogy to 10 per cent. By contrast

the mortality was small but not insignificant in most of the acyanotic groups. It was highest in those with atrial septal defect but there were many older patients, some over 60 years of age. Simple pulmonary valvular stenosis was the group with most deaths in children.

Patent Ductus Arteriosus: A Distinctive Syndrome associated with a Wide Short Duct

By G. Aitken. In six of a series of 55 consecutive cases of patent ductus arteriosus a systolic thrill was palpable in the suprasternal notch, and a systolic murmur in the aortic area and in the neck vessels. These cases presented other features differentiating them from the majority. Disability was greater and all were moderately dyspnœic on exertion; five gave a history of repeated serious respiratory illness, and two of intermittent œdema of the ankles; and hæmoptysis, recurring cyanotic episodes, præcordial pain, and frequent extrasystoles had occurred in one or more of them.

All had a much wider pulse pressure than the mean value for the whole series, and all had distinct left ventricular enlargement demonstrable clinically and radiologically. Four showed the electrocardiographic changes of left ventricular hypertrophy and in two the pattern reverted to normal following operation. The characteristic basal murmur to the left of the sternum was long and harsh, occupying the whole of systole and followed by a more blowing diastolic murmur of varying length. In three cases a low-pitched apical diastolic murmur was audible. Pulmonary artery pressure was high in three of the four cases in which it was known: only in the youngest case did it approach normal. Operative closure by ligature or division of the duct was successfully performed in four cases with disappearance of the suprasternal thrill and aortic murmur, although in one case the murmur persisted for three months after operation. In all four cases, the duct was wide and short. In one the pulmonary artery pressure fell from 105 to 30 cm. saline following ligature of the duct.

At first, the presence of an aortic thrill and murmur suggested an associated aortic valvular or subvalvular lesion. Their origin, however, is uncertain; they may arise from the patent duct or from relative aortic stenosis or distortion secondary to increased left ventricular output. We now believe that their presence in a case of patent ductus arteriosus indicates a wide short duct with, initially, a large shunt through the pulmonary circuit and that such cases are likely to become seriously incapacitated, and to develop pulmonary hypertension. Their early recognition and operative relief is important before irreversible cardiac or pulmonary vascular changes occur.

The Clinical and Radiological Assessment of Pulmonary Arterial Pressure in Mitral Stenosis

By L. G. Davis, R. E. Steiner, B. D. van Leuven (*introduced*), and J. F. Goodwin. Published in full, *Brit. Heart J.*, **15**, 393, 1953.

Left Atrial and Pulmonary Venous Pressures in Mitral Stenosis

By R. G. Epps and Richard H. Adler (*both introduced by P. Wood*). Published in full, *Brit. Heart J.*, 15, 298, 1953.

The Value of Electrocardiography in the Assessment of Patients with Mitral Valvular Disease

By Hugh Fraser (*introduced*) and Richard Turner. A study has been made of the value of electrocardiography in the assessment of patients with mitral valvular disease with particular reference to 115 consecutive patients submitted to operation. In 100, mitral stenosis was the sole or predominant defect and valvotomy was carried out. In 15 mitral incompetence was predominant and most of them were subjected to a different procedure. The cardiographic findings are compared with the clinical, radiological, catheterization and operative observations.

Severe mitral incompetence may co-exist with normal electrocardiograms even though there is considerable left ventricular enlargement clinically and radiologically. In cases of mitral stenosis even minor cardiographic changes demonstrating the presence of left ventricular hypertrophy indicate that some important complication is present, and of these mitral incompetence is the most difficult to assess.

Criteria for the cardiographic diagnosis of right ventricular hypertrophy are reviewed and difficulties discussed. In our experience any cardiographic evidence of right ventricular hypertrophy has signified not

only that mitral stenosis was the predominant defect, but that it was severe in degree, that pulmonary hypertension was usually considerable, and also that the patient was likely to derive much benefit from valvulotomy.

However, cardiographic evidence of right ventricular hypertrophy was present in only 30 per cent of the patients in whom predominant mitral stenosis was confirmed at operation although presumptive evidence for right-sided enlargement was present in the majority. Similar observations have been made on post-mortem material. It is concluded that cardiographic changes only occur when right ventricular hypertrophy is considerable. Such evidence is found more often in patients with normal rhythm than in those with auricular fibrillation. Possible reasons for this are given.

Changes in the P waves and in axis deviation and the value of right-sided V leads are analyzed. Reference is made to changes suggesting myocardial ischæmia which were recorded during paroxysms of dyspnœa, to the difficulties caused by old rheumatic myocardial fibrosis and by bi-ventricular hypertrophy, and to post-operative pericarditis patterns. In some cases serial electrocardiograms recorded objective evidence of deterioration before, or of improvement after operation.

The Left Atrial Electrokymogram in Mitral Stenosis

By P. H. Davison and R. G. Epps (*introduced*). Movement of the posterior border of the left atrium was recorded electrokymographically in the right anterior oblique position in 29 patients with severe mitral valve disease and 10 control subjects. The patients with mitral disease were divided into three clinical classes: pure mitral stenosis, mitral stenosis with incompetence, and pure mitral incompetence. Confirmation of the clinical diagnosis was obtained in 23 by digital palpation of the valve at operation.

It was found possible to classify the electrokymographic records of atrial movement into four main types —undulatory, ventricular systolic expansion, ventricular systolic retraction, and absence of movement.

Undulatory movement of the auricular border showed a variable pattern from case to case, and was observed in the majority of the controls and in the minority of those with mitral disease.

Ventricular systolic expansion was shown electrokymographically by a single positive wave, flat-topped or peaked and occupying the whole of ventricular systole, which represented an abrupt sustained backward movement of the posterior atrial border. This pattern was recorded in three-quarters of the patients with pure mitral stenosis, in an equal proportion of those with mitral stenosis and incompetence, and in both cases of pure incompetence. It appeared to be unrelated to the type of mitral valvular lesion, the degree of right ventricular hypertrophy, the left atrial pressure, or the left atrial pulse pressure, but occurred with greatest frequency when mitral disease was complicated by auricular fibrillation.

It has been concluded that electrokymography of the left atrial border movement provides no help in differentiating between pure mitral stenosis and mitral stenosis with incompetence.

The Left Auricular Appendage in Mitral Stenosis

By Florence McKeown. Published in full, *Brit. Heart J.*, **15**, 433, 1953.

Circulation in Aortic Stenosis

By R. Gorlin, I. K. R. McMillan, M. B. Matthews, and W. E. Medd, (*introduced by R. Daley*). Nine patients with clinical evidence of aortic stenosis (eight of whom had an aortic diastolic murmur) were studied at rest by cardiac catheterization: observations were made in seven of these during exercise. (Only one patient had a mitral diastolic murmur; post mortem the mitral valve admitted two fingers and was competent). Cardiac outputs were measured by the Fick method. Pulmonary artery, pulmonary capillary, right atrial and brachial artery pressures were recorded, both phasic and mean. Pulmonary capillary diastolic pressure was used as an index of left ventricular diastolic pressure. The left ventricle and stenosed aortic valve of two patients who subsequently came to necropsy were perfused in the pump system described by McMillan, (McMillan *et al.* (1952), *Brit Heart J.*, **14**, 42). The stenotic and regurgitant valve areas were measured from motion pictures taken during perfusion under simulated *in vivo* conditions.

Three observations were considered to be of importance.

1. Prolonged systolic upstroke, as compared with total systole, in the brachial artery tracing.
2. Increased amplitude of the " a "wave in the pulmonary capillary tracing.
3. Increased amplitude of the " a " wave in the right atrial tracing.

Pulmonary " capillary " diastolic pressure was normal at rest in four patients; in all it was abnormally high on exercise. In four patients the right atrial pressure was increased at rest; in all it rose on exercise.

In the two patients * in whom the valve areas were measured total cardiac output and left ventricular systolic mean pressures were calculated from hydraulic formulæ. From the data, total work of the left ventricle and its relationship to diastolic filling pressure could be calculated. These data were presented.

A short film showed the movements of the aortic valves which were measured at necropsy.

Cardiac Calcification

By D. Pyke and C. Symons (*both introduced by J. McMichael*). In a random survey of 400 men over the age of sixty, 27 cases of cardiac calcification were detected by X-ray screening. A film was shown composed of cineradiographs of calcified aortic and mitral valves, of calcified left and right coronary arteries, and of calcification of the pericardium, showing the position and movement of these structures during life. The patients with aortic and mitral valvular calcification had the clinical signs of valve disease, but the patients with coronary artery calcification showed neither clinical nor cardiographic signs of heart disease.

The Cardiac Output during Exercise and Recovery in Normal Subjects and in Patients with Rheumatic Heart Disease

By K. W. Donald, J. Bishop (*introduced*), and O. L. Wade. A technique whereby the cardiac output can be estimated from minute to minute during changing states is described. The behaviour of the cardiac output during exercise and recovery has been studied in normal subjects and in patients with rheumatic heart disease at different levels of work. The achievement or otherwise of a relatively steady state during short periods of exercise has been particularly investigated. The minute to minute changes caused by exercise in mixed venous and arterial blood saturation, in oxygen uptake, and in ventilation and ventilatory equivalent in different patients with mitral valvular disease are described and discussed.

The Pulmonary Early Systolic Click

By Aubrey Leatham and Louis Vogelpoel (*introduced*). We have investigated 50 patients in whom we heard an early systolic sound in the pulmonary area. This sound was of click-like or snapping quality and louder in expiration; occurring soon after the first heart sound it gave the impression of wide splitting of the first sound but was louder in the second and third left intercostal spaces rather than the mitral and tricuspid areas. The presence of this sound in early systole was confirmed by phonocardiograms in every case.

Of the 50 patients showing this physical sign on auscultation, 44 had pulmonary hypertension, either primary (3) or associated with a septal defect (24), with transposition of the great vessels (1), or with mitral stenosis (16). All but three of these 44 cases had obvious enlargement of the pulmonary trunk. Of the remaining 6, 2 had septal defects with dilatation of the pulmonary trunk but without pulmonary hypertension, 2 had slight pulmonary valve stenosis with dilatation of the pulmonary trunk, one had a faint pulmonary diastolic murmur and slight dilatation of the pulmonary trunk, and in the single remaining patient there was no evidence of heart disease. We conclude that the pulmonary early systolic click is a sign of dilatation of the pulmonary trunk especially when due to pulmonary hypertension.

The Effect of Exercise in Hypertension and the Modification of this Effect by Hexamethonium

By P. B. S. Fowler and A. Guz (*introduced by K. Shirley Smith*) In hypertension, the effect of exercise on the blood pressure has not been elucidated. It has been assumed, but never proved, that sympathectomy cuts out the peaks of a fluctuating pressure even when there is little change in the resting figures.

It was, therefore, decided to study the effect of exercise on the blood pressure. Hypertensive patients have had their blood pressure recorded during and after exercise on an ergometer. The effect of exercise on the pressure is found to be modified by hexamethonium bromide. Similar observations have been made on patients who have had the operation of sympathectomy and on controls.

* The catheter findings in one patient were provided by the Guy's Hospital team to whom we are grateful for permission to use them.

Myocardial Fibrosis of Unknown Cause

By W. G. A. Swan, and B. E. Tomlinson (*introduced*). Three cases of fibrosis of the myocardium of unexplained aetiology have come to autopsy in 1952. One died suddenly and there was no history of antecedent ill health. The remaining two were under observation for heart failure and were investigated before death. One of these patients had a father who died of unexplained heart failure; his electrocardiogram, taken in 1935, closely resembled that of his son taken in 1952. Otherwise there was no clear history of familial heart disease and none of Friedreich's ataxia.

All the three hearts examined showed severe and diffuse myocardial fibrosis without any inflammatory reaction. The appearances closely resembled those described by Evans in 1948. The coronary arteries were all healthy and there was no valvular disease. In the patients seen before death there were low blood pressures and general cardiac enlargement: the electrocardiograms showed low QRS voltage and low abnormal T waves. On the basis of similarity to these two patients, the diagnosis of myocardial fibrosis of unknown cause has been made tentatively in two other cases.

Wolff-Parkinson-White Syndrome with Paroxysmal Ventricular Tachycardia

By D. Robertson. Two cases of Wolff-Parkinson-White Syndrome with paroxysmal ventricular tachycardia are recorded. This is a rare combination.

One, a man, who was seen in an attack fifteen years ago, is now fit and well and has had no major attack during the past ten years. No structural heart disease is evident.

The other, a woman, was watched for four years while her attacks of paroxysmal tachycardia became progressively worse and more frequent; she eventually died, of ventricular fibrillation (in 1951). Partial post mortem was performed, including histology of the heart (by Prof. Hewer, at Bristol), and no accessory auriculo-ventricular muscular connection was apparent.

Arrhythmias Following Cardiac Infarction

By H. E. S. Pearson. In a series of 567 cases of cardiac infarction there were 202 instances of disturbance of rhythm in 144 patients. Of these 50 subjects showed more than one variety of arrhythmia and 7 more than two varieties.

The blood supplies to the sinu-atrial node, the A-V node, and the bundle are derived mainly from the larger circumflex vessel but the comparative rarity of severe ischæmic damage to these structures gives clinical confirmation of the presence of important subsidiary channels and a rich anastomosis. Complete functional destruction has always corresponded with lesions of both coronary arteries and a high mortality. Auricular flutter has occurred 7 times in similar circumstances.

Auricular fibrillation and the tachycardias were common but showed no relationship to the site of the infarct. They occurred generally in the more severe case. Multiple, and especially multifocal ectopic beats were associated with a mortality that was disproportionate to the apparent initial severity of the lesion. 18 of the 78 patients dying suddenly and unexpectedly.

Disturbances of rhythm after infarction are readily influenced by drugs, but the changing nature of the underlying cellular pathology makes the response to drug treatment variable and a dangerous ventricular excitability is often present.

The Plasma Lipids in Coronary Artery Disease

By M. F. Oliver and G. S. Boyd (*introduced by Rae Gilchrist*). Published in full, *Brit. Heart J.*, **15**, 387, 1953.

ABSTRACTS OF CARDIOLOGY

Edited by J. L. Lovibond in collaboration with Abstracts of World Medicine

Chronic Cardiac Compression (Chronic Constrictive Pericarditis). A Critical Study of Sixty-one Operated Cases with Follow-up. J. R. CHAMBLISS, E. J. JARUSZEWSKI, B. L. BROFMAN, J. F. MARTIN, and H. FEIL. *Circulation*, **4**, 816–835, Dec., 1951.

The authors present a study of the results of pericardiectomy for chronic cardiac compression in 61 patients (48 of them men).

Dyspnœa, ascites, and œdema were the primary complaints, and had been present, on an average, for 1 to 2 years. Distension of the neck veins was universal. Of the patients, 14 had auricular fibrillation. All had primary T wave changes in the electrocardiogram. Marked diminution of cardiac pulsation was found on radiological examination in all cases. Pleural effusion occurred in 49 of the patients.

In 26 cases calcified pericardium was obvious at operation, and in 12 cases signs of active infection of the pericardium, œdema, tubercles, or pus were seen. There were 11 deaths, and case histories of these patients are given. The condition of 6 patients was not improved and a further operation was necessary. Results regarded as excellent were obtained in 38 cases. Many cases showed a drop in venous pressure almost immediately after operation; and there was an increase in the stroke volume, most marked in the early post-operative period.

The authors finally discuss the ætiology of chronic constrictive pericarditis as revealed by their cases. In all of them a thick, adherent scar was found, in 2 concentrated in localized bands. Calcification was present in 50%. In 18 patients the cause was tuberculosis, and 35 cases were classified as being of unknown ætiology.

F. B. Cockett

The Heart and the Thyroid: with Particular Reference to ^{131}I Treatment of Heart Disease. H. L. BLUMGART and A. S. FREEDBERG. *Circulation*, **6**, 222–237, Aug., 1952.

This is a good article in which the use of radioactive iodine (^{131}I) in the treatment of heart disease is described in detail. With this treatment the therapeutic effect is said to be achieved through the production of hypothyroidism, which appears 6 to 26 weeks after giving the ^{131}I, its onset coinciding with great clinical improvement. It is recommended that the treatment be reserved for severe cases of heart disease and those in which the condition is not rapidly progressive; it should be combined with the usual medical measures. Enough thyroid is given to allow the maximum beneficial effect of the lowered metabolic level on the heart and the minimum of discomfort arising from the hypothyroid state.

Of 26 patients with severe and intractable angina pectoris given treatment with ^{131}I worthwhile results were obtained in 19. In 9 of these 19 patients the angina practically disappeared, and 4 of them have been able to return to work. Treatment with ^{131}I was also given to 13 patients with congestive heart failure, worthwhile improvement being obtained in 6 of them.

G. S. Crockett

Angiocardiography in Mitral Disease. A. ACTIS-DATO, P. F. ANGELINO, and E. ZAMBELLI. *Minerva med., Torino*, **43**, 693–713, 1952.

The angiocardiogram of the normal heart is discussed. In mitral stenosis the superior vena cava and right auricle may be slightly increased in size, while the right ventricle is nearly always larger than normal; the pulmonary conus is enlarged in its transverse diameter and appears convex instead of rectangular. Thus the normal U shape is lost and in addition opacification may persist for as long as 8 seconds. The branches of the pulmonary artery are irregular, tortuous, and fragmented and the pulmonary veins dilated and well-marked; the dye may persist in the pulmonary vessels until the end of the examination. The left auricle is the size of an orange or larger and is intensely and persistently opacified; the left ventricle can be seen as a small, poorly filled shadow below it. Opacification may persist in the left side of the heart for up to 20 seconds after the injection of the dye.

The authors believe that they can distinguish mitral incompetence by two features: (1) the left auricle and left ventricle are equally opacified; and (2) the left ventricle is larger than normal. The abnormalities in the pulmonary vascular tree, together with persistent opacification and the delayed visualization of the left auricle, suggest pulmonary hypertension. *A. Paton*

Fundamentals of Clinical Fluoroscopy. CHARLES B. STORCH, M.D. Adjunct, Radiodiagnostic Department and Radiotherapy Department Beth-El Hospital, New York. London: William Heinemann, 1951. Pp. 196. Illus. 217. 50*s*.

In a simple and practical manner, with lucid diagrammatic illustrations, the author describes the principles, procedure and interpretation of radioscopic examination. Approximately one half of this well produced, but expensive small book is concerned with the heart and chest; the remainder deals with the radioscopy of the gastrointestinal tract. An authoritative clinical approach flavours its pages, which portray with considerable clarity the fundamental value of this useful diagnostic method both in health and in disease.

J. L. Lovibond

Röntgenatlas der Erkrankungen des Herzens und der Gefässe. WALTER BREDNOW, Director of Medicine, University Clinic, Jena. München: Urban and Schwarzenberg, 1951. Pp. 223, DM., 22*s*.

An individual collection of some 120 exquisitely reproduced X-ray films of some of the commoner cardiac abnormalities annotated with explanatory texts of reasonable brevity. The author adopts the method of comparing suitable cases with plaster casts of the heart and with kymograms. Myocardial failure, valvular disease, pericardial, aortic and peripheral arterial conditions are dealt with but congenital disorders are not included, and there is no index. *J. L. Lovibond*

The Frequency of Functional Heart Disturbances. A Study of 1000 Consecutive Private Cardiac Patients. A. M. MASTER. *J. Amer. med. Ass.*, **150**, 195–198, Sept. 20, 1952.

Of 1000 consecutive patients seen in consultation practice, three-fourths of whom lived in New York City, 382 were found on fluoroscopic and electrocardiographic examination to be suffering from functional "disturbance" of the heart (which term is preferred to "disease"). Of the patients, 289 were men and 93 were women, the majority being under 50 years of age, whereas the majority of patients with arteriosclerotic heart disease are over 50.

Pain or pressure in the chest was the commonest symptom and was found in 64 per cent of cases, occurring alone in 171 patients, and in conjunction with other functional disturbances in 72 others. Occasionally the pain was indistinguishable from that of coronary disease. Paroxysmal tachycardia was found in 50 patients, premature beats in 18, neurocirculatory asthenia in 48, anxiety neurosis in 13, hypertension in 17, and murmurs in 12. A group of 53 patients was classified as "miscellaneous." Chest pain was present in 42 per cent of the patients with paroxysmal tachycardia, which was sino-auricular in type. The functional murmurs were all systolic in time. There was no instance of ventricular tachycardia or of a Grade 3 murmur. "Sighing" was often mistaken by the patients for shortness of breath.

The treatment of these functional disturbances of the heart is often unsuccessful, but it is hoped that recognition of their frequent occurrence will lead to research into their causes with a view to their prevention or cure. *R. R. Willcox*

Congenital Pulmonary Stenosis without Cyanosis. J. J. GALLIGAN, F. H. ADAMS, and J. JORGENS. *J. Pediat*, **41**, 562–571, Nov., 1952.

From the Universities of California and Minnesota the authors give an account of the clinical features of 23 cases of pulmonary stenosis without cyanosis, in 20 of which the diagnosis was confirmed, by cardiac catheterization in 17 cases and by surgical exploration in 3. The 12 male and 11 female patients ranged in age from 20 months to 29 years, but 15 of them were under 15 years of age. Most of these patients appear to be normal at birth and a heart murmur is usually found some time later at a routine examination. Development is normal, but about half the patients develop dyspnœa of some degree by the age of 15. The degree of stenosis determines the disability and prognosis, and death results from either heart failure or subacute bacterial endocarditis. Isolated pulmonary stenosis is a relatively common cardiac defect.

In the cases here presented cyanosis was absent in all. Electrocardiography showed evidence of right ventricular hypertrophy in 18 of the patients. The results of catheterization are summarized. All the cases were considered to be of the valvular type of stenosis, and 11 patients were treated by pulmonary valvotomy; of these one died, but the remainder appeared to have benefited from surgery. *James W. Brown*

On some Aspects of Unipolar Electrocardiography in the Presence of Pulmonary Pathology. T. T. FOX, H. BERGER, and C. E. MEIDT. *Amer. Heart J.*, **44**, 747–753, Nov., 1952.

An analysis of 100 abnormal electrocardiograms obtained from patients with pulmonary tuberculosis showed that in four cases only were the abnormalities indicative of myocardial damage, being apparently due to mediastinal shift and rotation in the remainder. Although the unipolar leads provided no evidence of myocardial damage that was not discernible in standard leads, they were of value in clarifying abnormalities in the standard leads and in providing evidence of mediastinal shift and rotation in cases in which the standard leads appeared normal. Attention is drawn to mediastinal displacement as a cause of RS–T deviation, which should not, therefore, be regarded as pathognomonic of myocardial damage. One pattern which occurred particularly frequently in cases with mediastinal displacement consisted of an inverted P wave, an R wave, and an inverted T wave in aV_L, being found in 22 records; this was totally independent of the pattern of aV_R which was often of the QS or rS type. In none of the 22 cases in which this aV_L pattern was found was there any clinical evidence of cardiovascular disease. *William A. R. Thomson*

The Intramuscular Use of Pronestyl (Procaine Amide). S. BELLET, S. E. ZEEMAN, and S. A. HIRSH. *Amer. J. Med.*, **13**, 145–157, Aug., 1952.

From the University of Pennsylvania the authors report a study of the effects of pronestyl gluconate and hydrochloride given intramuscularly in single and multiple doses to normal subjects and to patients with congestive heart failure or ectopic rhythms.

It was found that pronestyl given by intramuscular injection was satisfactorily absorbed, a peak serum level of the drug being obtained in 15 minutes to 1 hour. This is a quicker rate of absorption than is obtained by oral use of the drug, but slower than when it is given intravenously. The toxic effects which may occur with intravenous administration, such as severe hypotension, are, however, absent with intramuscular injection, although there may be a slight fall in blood pressure.

In the doses adopted, which ranged from 0·5 to 1·0 g. given as a single dose or in multiple doses, there was some evidence that cumulative effects may occur with repeated injection of the larger amount. In most of the patients with arrhythmia the optimal level of serum concentration of pronestyl appeared to be about 0·5 mg. per 100 ml. The drug was found to be of value in ventricular tachycardia, nodal tachycardia, and some cases of auricular tachycardia; it also reduced the frequency of, or abolished, ectopic beats. The authors state that if a therapeutic effect is to occur at all, it is usually manifest within half an hour of intramuscular injection. The treatment may convert some cases of flutter to a normal rhythm, but is without influence on auricular fibrillation. *James W. Brown*

Mitral Stenosis with Long-lasting Congestive Heart Failure or Auricular Fibrillation. D. E. Love and S. A. Levine. *New Engl. J. Med.*, **247**, 917–920, Dec. 11, 1952.

From an analysis of the records of 510 patients who died from mitral stenosis in the Peter Bent Brigham Hospital, Boston, between 1913 and 1946 and the records of 164 patients with mitral stenosis who attended the out-patient department between 1940 and 1942, the authors found that 65 patients had survived 9 or more years after the onset of objective evidence of congestive heart failure or permanent auricular fibrillation. The average interval from onset of rheumatic fever to onset of congestive failure or auricular fibrillation was 23 years and 25 years respectively. The authors consider that in general about 10 to 13% of all patients with mitral stenosis survive 9 or more years after onset.

Tricuspid stenosis, which occurs in only 10% of all cases of rheumatic heart disease, was present in 15 of the 65 cases in this series. Hypertension was noted in 32 patients (the authors believe, with others, that hypertension has a protective role in these cases, but the present investigation did not afford any opportunity to prove this). In some of the cases neither of these conditions was present, but the patients were "long-survivors." The authors state that the possibility of such survival must be borne in mind when selecting patients for valvotomy. *R. S. Stevens*

Post-operative Changes in the Electrocardiogram in Mitral Stenosis. P. Soulié, F. Joly, J. Di Matteo, and G. Folli. *Cardiologia, Basel*, **21**, 665–674, 1952.

In a study of 34 cases of mitral stenosis treated surgically it was found that while in some cases some or all of the electrocardiographic signs of mitral stenosis disappeared after valvotomy, in others the tracing remained virtually unchanged. However, it was demonstrated that signs of right ventricular hypertrophy and strain persisted only in those cases in which postoperative cardiac catheterization suggested that there was no improvement in the hæmodynamics of the heart over the preoperative condition. *G. Schoenewald*

Electrocardiographic Changes After Commissurotomy in Mitral Stenosis. [In English]. V. Puddu, L. Comberiati, and A. Collicelli. *Cardiologia, Basel*, **21**, 657–664, 1952.

A study was made of the electrocardiographic changes occurring in 24 patients after valvotomy for mitral stenosis at the Polyclinic, Rome. The disappearance of signs of right axis deviation and right ventricular strain was found to run parallel with clinical improvement. *G. Schoenewald*

Studies in Mitral Stenosis. IV. The Relative Merits of Various Diagnostic Methods in Mitral Valvular Disease. G. Björck, O. Axén, H. Krook, L. Andrén, and H. B. Wulff. *Amer. Heart J.*, **45**, 13–39, Jan., 1953.

With the introduction of surgical techniques for the relief of mitral disease the differentiation between predominant stenosis and predominant regurgitation has greatly increased in importance, and the authors here re-examine the principles on which that differentiation must be based. In pure mitral stenosis there is distension of the left auricle with a left ventricle of normal size, a typical "stenotic" murmur, an increase in pressure in the left auricle and the pulmonary veins in auricular systole, and a slow circulation through the lungs. In pure mitral regurgitation the left auricle and left ventricle are both enlarged, there is a loud systolic murmur, a systolic pressure wave is found in the left auricle and the pulmonary veins, and although pulmonary circulation is not necessarily delayed, blood may accumulate in the left side of the heart. To distinguish between the two it is necessary therefore to determine the size of the left ventricle, the character of the murmurs, the volume of the left auricle, the changes of pressure in the pulmonary veins, and the way in which the blood passes through the pulmonary circulation and the left heart. The diagnostic methods available include palpation of the apex beat, auscultation, electrocardiography, radioscopy, angiocardiography, electrokymography, and cardiac catheterization with the recording of pulmonary capillary venous (p.c.v.) pressure tracings.

The relative value of these procedures has been tested in 25 cases of mitral disease referred to the authors for possible surgical treatment, the conclusions arrived at by each method being compared with the findings either at operation or at necropsy. In this way the accuracy of the information obtained was assessed, enabling the procedures used to be placed in the following order of diagnostic value: auscultation, radioscopy, angiocardiography and electrokymography, unipolar chest electrocardiogram (ECG), palpation of the apex beat, electrical axis in the standard ECG, and p.c.v. tracings. The ECG was found to give only minor help, signs of right axis deviation indicating some complication, but the finding of a normal axis being of no significance.

As the character of the murmurs proved the most helpful diagnostic index, the authors suggest that greater attention be paid to the subject of their evaluation. It is in patients with systolic murmurs of Grades II and III (Levine) that further investigation is necessary to determine whether there is significant mitral regurgitation or not. *Arthur Willcox*

Surgical Treatment of Aortic Stenosis. C. P. Bailey, H. P. Redondo Ramirez, and H. B. Larzelere. *J. Amer. med. Ass.*, **150**, 1647–1652, Dec. 27, 1952.

Aortic stenosis is usually the result of rheumatic fever or arteriosclerotic changes in the root of the aorta. In the former case the commissures of the valve cusps fuse and the orifice is reduced to a small opening which, with fibrosis, becomes a rigid ring, so that both stenosis and regurgitation are present. There is a tendency for the fusion of the anterolateral cusps to be more marked than elsewhere, and the aortic valve is often transformed into a bicuspid mechanism with a rigid and large anterior part and a smaller, more mobile, posterior flap. Severe aortic stenosis is associated with a poor coronary blood supply, gross enlargement of the left ventricle, and serious strain on the myocardium.

Surgical treatment of the condition was first attempted by Tuffier in 1913, who dilated a stenosed valve with a finger by invaginating the loose anterior aortic wall. The present authors, first tried to treat the conditions by incising the stenosed valve; this was inevitably followed by some degree of regurgitation, which was poorly tolerated and even led to sudden death on one occasion. Their efforts were then directed towards dilatation, in the hope that the commissures might be split open and part of the valve action restored. An umbrella-like dilator passed through the ventricular wall was used in 11 cases, the dilator being guided into the stenosis and then opened. There were 2 deaths in hospital and 2 subsequent deaths, but improvement was noted in the remainder.

More recently an improved expanding dilator has been used which is threaded over a guide wire previously passed through the stricture, the incision into the ventricle being controlled by a purse-string suture. While it is essential to establish an adequate passage-way, it is necessary to avoid excessive dilatation which might not only lead to increased regurgitation, but might even rupture the aortic wall. An opening of half the normal size will give complete clinical relief, the orifice in severe cases of aortic stenosis being usually about 10% of normal before treatment.

The new instrument has been used successfully in 9 cases, 6 patients having undergone the combined operation and 3 others aortic dilatation only.

T. Holmes Sellors

The Indications for and the Results of Commissurotomy for Mitral Stenosis. R. P. Glover, T. J. E. O'Neill, J. S. C. Harris, and O. H. Janton. *J. thorac. Surg.*, **25**, 55–77, 1953.

This article is based on the results of 256 operations for mitral stenosis in which there were 14 operative deaths, a mortality of 5·4%. Of the 242 survivors, 164 were followed up for at least 6 months, and are analysed in detail.

In selecting cases for operation it is essential that mitral stenosis be the predominant lesion in producing the disability, but minimal mitral regurgitation is not a contraindication to surgery, nor is insignificant aortic valve disease. In many patients with auscultatory evidence of mitral insufficiency no regurgitant jet could be felt at operation. Enlargement of the left ventricle tends to contraindicate operation, and enlargement of all chambers does so absolutely. Auricular fibrillation is no bar unless the rate is uncontrolled. A high pressure in the pulmonary artery is usually associated with severe symptoms, with left atrial, right ventricular, and pulmonary arterial enlargement, and with right axis deviation in the electrocardiogram. In general, when estimations were made by cardiac catheterization before and after operation, there was a subsequent fall of pressure, averaging 15 mm. Hg after one month, with a further fall later, and paralleling symptomatic relief. The electrocardiogram assists diagnosis; left axis deviation contraindicates surgery.

At operation the valve orifice was usually 0·5 to 1 cm. in diameter. A small cut in the antero-lateral commissure was followed by gentle digital pressure, a further cut being made if necessary. Often a small cut was also made in the postero-medial commissure, but extensive division on this side led to serious regurgitation, and recently no division has been made where the antero-lateral division produced an adequate orifice. When thrombus was present the knife was not introduced. Nearly half the valves were calcified, particularly in the medial part of the anterior cusp; this did not of itself prevent a good result. In nearly one-quarter of the patients there was evidence of thrombosis in the appendage, but few of these had had emboli.

Of the 164 patients, 125 were improved, 80 being classed as "excellent," and enjoying normal activities without limitation; 20 were not improved, but many of these had regurgitation before operation. Among those followed up there were 10 operative deaths (5 from technical faults), and 9 late deaths, all but one occurring in patients in Stage V, that is, in the extreme terminal state. It is suggested that the ideal patient for operation has isolated mitral stenosis and is beginning to have symptoms of cardiopulmonary disfunction.

In the discussion following the paper, Bailey described precautions taken to avoid cerebral embolism, consisting of temporary occlusion of the left common carotid artery by a tape passed round it in the mediastinum, and of the innominate artery by a bulldog clamp across its origin.

M. Meredith Brown

Follow-Up Studies on the First 1,000 Patients Operated on for Pulmonary Stenosis or Atresia. Results Up to March 1952. H. B. Taussig and S. R. Bauersfeld. *Cardiologia (Basel)*, **21**, 541–551, 1952; *Ann. intern. Med.*, **38**, 1–8, Jan., 1953.

This report is concerned with 1000 patients who have been operated on since November, 1944, by Blalock and his associates by systemic–pulmonary vascular anastomosis, and who have been followed up (except for 6% who could not be traced) for at least 18 months, and in the earliest cases for over 7 years.

"Good" results—defined as marked decrease of cyanosis, rise of arterial oxygen saturation, and subjective improvement—were obtained in 773, and "fair" results —improvement, but with persistent cyanosis and polycythæmia—in 39, while 31 were unimproved; 157

of the patients died at or immediately after operation, an immediate fatality rate of 15·7%.

The majority of the patients (857) were diagnosed before operation as having tetralogy of Fallot; the next most frequent diagnoses were tricuspid atresia (62) and pseudotruncus arteriosus (27). It was later shown that in 40 cases the diagnoses made were incorrect; 29 of these patients died at or shortly after operation. Of 5 patients who later were found to have pulmonary stenosis with an intact ventricular septum, all developed right-sided cardiac failure after their operation; in these cases pulmonary valvotomy would have been a better treatment. Patients with Fallot's tetralogy had the lowest immediate mortality (15%) and the highest proportion of good results (78%), and in addition they developed cardiac failure after operation less often. If cardiac failure is to develop it usually does so within 6 months. In 15 of the patients with Fallot's tetralogy, the aorta over-rode the ventricular septum by more than 50%; all these patients died at operation, or shortly after, from pulmonary congestion. The extent of over-riding cannot be diagnosed accurately. In the cases with Fallot's tetralogy the delayed mortality was 6%, but in those with a good operational result was only 4%, and in a number of these cases death was not due to the cardiac malformation. The vast majority of these patients are able to adjust to the altered circulation. Those who failed to maintain their improvement (16%) have either died, or have had or are awaiting a second operation, but such operations carry a high fatality rate.

The patients with atypical malformations showed results somewhat less favourable but of the same order; and again the prognosis in those with a good result from operation was notably better than in those with only a fair result. The incidence of subacute bacterial endocarditis was low—22 cases with 4 deaths. Half of these cases occurred within 2 months of operation, confirming the authors' opinion that in the early postoperative period these patients are extremely susceptible to bacterial endocarditis, and it is therefore recommended that large prophylactic doses of penicillin be given. The additional anomaly does not, however, subsequently appear seriously to increase the patients' susceptibility to endocarditis.

[This important article contains detailed statistics and analyses of results.] *M. Meredith Brown*

A Method for Surgical Closure of Intrauricular Septal Defects. R. E. Gross, E. Watkins, A. A. Pomeranz, and E. I. Goldsmith. *Surg. Gynec. Obstet.*, **96**, 1–23, Jan., 1953.

The indications for closure of an atrial septal defect are briefly discussed, and a description of the various operations designed to alleviate this defect is given. The authors then describe in detail their technique, in which the "atrial-well" principle is used to obtain direct access to the interior of the chamber (Gross *et al.*, *New Engl. J. Med.*, 1952, **247**, 455). Three methods of closure of the atrial defect have been used: (*a*) a Hufnagle double disk button, which engages the edges of the gap; (*b*) suture of a sheet of plastic material to the edges of the defect; (*c*) direct suture of smaller defects.

Details are given of 7 cases in which the operation has been performed. Three patients treated with the button all died, largely because the disks became dislodged owing to the fact that the rim of the septal defect was not adequate for contact of the disk around its whole circumference. Of the other 4, one was treated by direct suture and did well, the remaining 3 being treated by suture of a nylon membrane over the defect. Of these one died owing to the formation of a thrombus under a redundant piece of the plastic material, but the other 2 were much improved. *J. R. Belcher*

Congenital Interatrial Communications: Clinical and Surgical Considerations with a Description of a New Surgical Technic: Atrio-septo-pexy. C. P. Bailey, D. F. Downing, G. D. Geckeler, W. Likoff, H. Goldberg, J. C. Scot, O. Janton, and H. P. Redondo-Ramirez. *Ann. intern. Med.*, **37**, 888–920, Nov., 1952.

In view of the unfavourable course in many cases the question of surgical closure must arise where the defect is thought to be the principal cause of the disability. A number of operations have been devised for closing an opening in the interatrial septum: fascial strips or stout ligatures have been inserted along the line of the septum and tightened, invagination of the atrial wall with suture of this to the edge of the defect has been tried, and plastic prostheses have been introduced. Some of these procedures have been applied clinically, but each has certain disadvantages. The authors have operated in 10 cases, in the first 9 of which Swan's technique of closure by invagination of both atrial appendages was carried out or attempted; there were 6 deaths at or shortly after operation, and in the survivors the results were not thought to be sufficiently satisfactory to justify continuation of this or any similar procedure. A new operation was therefore devised to which the title of "atrio-septo-pexy" is given and which has been performed successfully in one case. The principle of the operation is to suture the wall of the dilated right atrium to the edges of the defect, the procedure being helped, and indeed made possible, by insertion of the left index finger through the right atrial appendage into the defect as a guide in placing the sutures through the atrial wall and the edge of the defect, the wall being then drawn into close approximation to the margin of the defect and completely sealing it. The pre-existing dilatation of the right atrium enables this to be done without producing too narrow a venous inlet. There was complete relief of symptoms with no evidence of any residual shunt after the operation in the case described. *T. Holmes Sellors*

The Anatomy of Fallot's Tetralogy. G. C. Berri, J. A. Caprile, and R. Kreutzer. *Arch. Mal. Cœur*, **45**, 1082–1091, 1952.

The authors have analysed the anatomical features of the cardiac abnormality in 19 cases of Fallot's tetralogy.

There were 5 cases of infundibular stenosis only, and one of pure valvular stenosis at the pulmonary orifice. In the remaining 13 cases of the classic tetralogy both infundibulum and valve were stenotic. This stenosis was

very severe in 3 cases, amounting in one to complete atresia. The authors found that the orifice of the stenosed infundibular chamber may be buried in the papillary muscles and ridges of the wall of the right ventricle, and that its axis may form an angle with that of the pulmonary artery. In about one-third of the cases this chamber constituted a virtual " third ventricle " which would add greatly to operative difficulties. An associated hypoplasia of the pulmonary artery, if present, may prevent a good functional result if pulmonary valvotomy is undertaken.

Among the associated abnormalities present, a right-sided aorta was found in 9 cases, interatrial communication in 7, patent ductus arteriosus in 4, and anomalies of the arteries arising from the arch in 3. A left superior vena cava, opening into the right auricle through the coronary sinus, was present in 3 cases. In one case there was a single coronary trunk, arising from the aorta and soon dividing into 2 branches. *D. Weitzman*

An Anatomical and Clinical Study of Tricuspid Stenosis. P. CHICHE. *Arch. Mal. Coeur*, **45**, 980–1015, Nov., 1952.

This is a detailed account of the anatomy of the different types of tricuspid stenosis, together with their clinical, electrocardiographic, radiological, hæmodynamic and angiocardiographic features, and finally the place of surgery in this condition. The report is based on 14 personal cases coming to necropsy at the Hôpital des Enfants Malades, Paris, and on 5 further clinical cases, and on hospital records.

The essential difference between the various types lies in the 4 different routes by which blood reaches the lungs from the left ventricle. Out of 70 recorded cases it was shown that the blood passed by way of: (1) a ventricular septal defect and the pulmonary artery in 45 cases; (2) a patent ductus arteriosus in 6 cases; (3) via the pulmonary artery, associated with transposition of the great vessels, in 9 cases; or (4) via a patent ductus arteriosus, associated with transposition of the great vessels and pulmonary atresia, in 10 cases.

Tricuspid stenosis was found in 17 (2·5%) of 700 cases of congenital heart disease, the majority of cases being seen in the first year of life.

Few patients lived to the age of one year, but a few did survive to adult life. Surgical intervention is recommended for those cases in which there is a deficient pulmonary circulation. *Keith Ball*

The Angiocardiographic Diagnosis of Coarctation of the Aorta. D. CATALANO, C. T. DOTTER, and I. STEINBERG. *Radiol. med. Torino*, **38**, 1129–1144, Dec., 1952.

The diagnostic value of angiocardiography in coarctation of the aorta is discussed with reference to a series of 51 cases studied at the University of Naples and at the New York Hospital–Cornell Medical Center. There were 31 male and 20 female patients, and 11 were under the age of 15 years. Excision and end-to-end anastomosis were carried out on 24 of the patients, and in 13 of these cases angiocardiography was repeated after the operation.

The arch of the aorta is often hypoplastic, and runs obliquely backwards and downwards. In the majority of cases the site of constriction is below the origin of the left subclavian artery (which is more distal than in the normal subject) and is angulated forwards and downwards by the insertion of the ligamentum arteriosum. The length and diameter of the constricted portion cannot be accurately estimated because of the superimposition, in the projection used, of the portions of aorta above and below it, but post-stenotic dilatation is invariably shown. However, the narrowness of the stricture is not reflected in any delay in the opacification of the post-stenotic portion: in some of the authors' cases the interval between injection and opacification of the descending aorta was the same after operation as before. The aorta below the post-stenotic dilatation appears normal.

The left subclavian artery is dilated, often having the same calibre as the aortic arch, and the internal mammary arteries are also very dilated and tortuous. An almost constant finding is of two vessels running up from the post-stenotic dilatation to link up with the costo-cervical axis: their accurate location by this method helps the surgeon to avoid damaging them. In cases of localized narrowing of the aortic arch without gross interruption of its lumen angiocardiography shows that the remainder of the aorta is normal, and no collaterals are to be seen. The postoperative angiocardiogram shows narrowing of the aorta at the site of anastomosis. The pre-operative dilatation of the great vessels persists and the collateral vessels remain distended and visible, but may be less well opacified than previously owing to the change in blood flow.

Illustrative angiocardiograms are reproduced, and the clinical features of the condition summarized.

D. Weitzman

Comparison of Cardiac Output Determined by the Ballistocardiograph (Nickerson Apparatus) and by the Direct Fick Method. R. T. CATHCART, W. W. FIELD, and D. W. RICHARDS. *J. clin. Invest.*, **32**, 5–14, Jan., 1953.

From comparative determinations made in 40 individuals comprising both normal subjects and patients with a variety of clinical conditions, the authors conclude that " the ballistocardiographic measurement of cardiac output gives such erratic results, with so many and such unpredictable errors from case to case, that it should no longer be used in any way whatever as an indication of this function." *A. I. Suchett-Kaye*

A Ballistocardiographic and Electrocardiographic Study of 328 Patients with Coronary Artery Disease; Comparison with Results from a Similar Study of Apparently Normal Persons. W. R. SCARBOROUGH, R. E. MASON, F. W. DAVIS, M. L. SINGEWALD, B. M. BAKER, and S. A. LORI. *Amer. Heart J.*, **44**, 645–670, Nov., 1952.

The authors report the electrocardiographic and ballistocardiographic findings in 191 cases of angina pectoris and 137 cases of healed myocardial infarction studied at Johns Hopkins Hospital, Baltimore, and compare them with those in 369 persons without cardiovascular disease.

Patients with conditions, other than coronary arterial disease, that might affect the findings, were excluded. In all cases a full electrocardiographic investigation was carried out; in some cases Master's two-step effort test was carried out in addition. Ballistocardiographic studies were carried out on a high-frequency bed, in most cases before and after abdominal compression.

The authors conclude that although ballistocardiographic abnormality is commonly found in coronary disease, its frequent occurrence in apparently normal subjects over the age of 50 cannot be assumed to be due to the presence of "silent" coronary disease. The effects of physiological ageing of the heart and circulatory system cannot as yet be evaluated.

J. F. Goodwin

Length of Survival After Myocardial Infarction. C. SMITH. *J. Amer. med. Ass.*, **151**, 167–170, 1953.

In 1942 the author and his colleagues published the results of a 10-year follow-up of 100 consecutive patients with coronary thrombosis (*Ann. intern. Med.*, **17**, 681), 66 of the patients being alive at the time of the report. In the present paper the author, working at Atlanta, Georgia, reports his findings after a further 10-year period. At the beginning of 1952, 16 of the original 100 patients were alive, 69 were known to be dead, and 15 were lost to follow-up.

The author states that according to the literature the average duration of life after myocardial infarction is 41·1 months; in his series 60 patients lived longer than this. Of the 35 patients who died between 1941 and 1952, 14 lived well into the second decade after the initial attack. No definite relation was observed between the age of the patient at onset and the survival time. Co-existing hypertension appeared to influence the survival time as did recurrent attacks of myocardial infarction. Of 30 patients followed-up for more than 10 years, 14 had hypertension before the onset of myocardial infarction, and 9 of these died; 13 of the 30 had a second or third attack of myocardial infarction and 9 of these 13 died. In cases in which there were persistent changes in the electrocardiogram the prognosis was poor. Cerebral vascular complications were common. No case of neoplastic disease was encountered in the series.

C. W. C. Bain

Prognosis in the "Uncomplicated" First Attack of Acute Myocardial Infarction. H. I. RUSSEK and B. L. ZOHMAN. *Amer. J. med. Sci.*, **224**, 496–499, Nov., 1952.

The high over-all mortality from acute myocardial infarction has created the impression that the prognosis is serious in every type of attack. It has, however, been reported by several authorities that the mortality resulting from a first attack of myocardial infarction may be as low as 8 to 8·5%, even without anticoagulant therapy. A series of 1047 cases of acute myocardial infarction admitted to three New York hospitals are here analysed in order to determine the prognosis in "uncomplicated" first attacks. The cases were divided into two groups; 558 with one or more unfavourable features (previous attack, intractable pain, extreme or persistent shock, significant enlargement of the heart, gallop rhythm, heart failure, auricular fibrillation or flutter, paroxysmal ventricular tachycardia, intraventricular block, severe diabetes, marked obesity, or any state obviously predisposing the thrombosis), and 489 "good risk" cases with none of these features. The total mortality was 33%, but whereas it was 60% in the former group, it was only 3% in the latter. Moreover, nearly one-half of the deaths in "good risk" cases occurred abruptly and within 48 hours of admission, the subsequent death rate from cardiovascular causes being only 1·2%. It is claimed, therefore, that anticoagulant therapy has no place in the treatment of "good risk" cases.

Paul Wood

Electrocardiographic Assessment of Posterior Cardiac Infarction. C. PAPP and K. SHIRLEY SMITH. *Amer. Heart J.*, **44**, 696–714, Nov., 1952.

The authors discuss the difficulties which arise in the diagnosis of posterior myocardial infarction of slight degree, and report the results of an investigation carried out at Charing Cross Hospital, London, into 100 consecutive cases of acute posterior infarction observed over a 2-month period. The cases were classified on clinical grounds as slight, moderate, or severe, while the initial electrocardiograms were arbitrarily divided into three groups according to the changes shown in R–T and T in leads II, III, and aV, those with R–T elevation and monophasic T waves being classified as "acute," those with bowing of the R–T interval and deep T-wave inversion as "subacute," and those with pathological Q waves, *iso*electric R–T intervals, and flat T-wave inversion as "chronic." An effort test was employed in cases in which the routine 12-lead tracings were equivocal.

Of the 100 patients, 22 had slight, 21 moderate, and 57 severe degrees of infarction, whereas in 150 cases of anterior infarction classified according to the same criteria the figures were 42%, 23%, and 35% respectively. The ratio of men to women was 4·6 to 1.

Both the effort test and the recording of leads III and aVF on inspiration (IIIR and aVFR) were helpful in confirming the presence of infarction in cases where the resting pattern was equivocal. Augmented T waves in leads II, III, and aVF in severe posterior infarction, accompanied by elevation of the R–T segment and preceding the development of abnormal Q waves in these leads, was seen in one case, and was associated with an uneventful recovery. The authors point out that this augmentation of the T waves in leads reflecting posterior cardiac potentials should not be confused with the reciprocal augmentation of the T wave in anterior leads, which nearly always occurred in severe posterior infarction; they found that the absence of such reciprocal changes indicated anterior extension of the infarct. The association of increasing anginal pain and signs of extending infarction in a patient with a slight initial attack was considered to be an indication for anticoagulant treatment.

[This excellent paper is well illustrated and should be consulted in the original by those specially interested in the subject.] *J. F. Goodwin*

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